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The Journal of Allergy

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The Journal of Allergy

VOL. 8 NOVEMBER, 1936 No. 1

Original Articles

A STUDY OF BLOOD CONSTITUENTS IN POLLINOSIS WITH AND WITHOUT TREATMENT*†‡

M. L. HATHAWAY, PH.D., B. Z. RAPPAPORT, M.D., C. I. REED, PH.D., AND H. C. STRUCK, PH.D.
CHICAGO, ILL.

IN EARLIER publications[1, 2] we gave accounts of the results of treatment during the seasons of 1932 and 1933 of hay fever and seasonal asthma with concentrated preparations of vitamin D in the form of viosterol (1,000,000 U. S. P. units per gm.). A similar series of cases numbering 240 was under observation and treatment during the summer of 1934, while an equal number was observed clinically during 1935.

During the 1933 season, 68 patients were treated with concentrated viosterol alone, while 144 patients received in addition to viosterol prophylactic injections of pollen extract. This study indicated that concentrated viosterol alone was of definite value in the relief of hay fever and asthma due to pollen. The combined use of viosterol and pollen treatment was, however, definitely more effective than the use either of pollen alone or of viosterol alone.

The clinical results of our study of 240 patients sensitive to the ragweed pollens who were observed during the 1934 season were so nearly like those of the 1933 season that it would be repetitious to go into statistical details so similar to our previous report. It may be of interest, however, to mention briefly one group of patients who were treated differently from those in our 1933 study. In this previous study 30 patients were given corn oil as a control against those receiving viosterol. Eighteen of these 30 dropped out before August 20, because of lack of benefit from the corn oil. The remaining 12 were then given

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†The expenses of this investigation were borne in part by grants from the Committee on Therapeutic Research of the American Medical Association, and from Mead Johnson and Company, and the Wisconsin Alumni Research Foundation. The vitamin D was supplied by Mead Johnson and Company.

‡Read before the Twelfth Annual Meeting of Association for the Study of Allergy, Kansas City, May, 1936.

viosterol. Criticism has since arisen regarding the advisability of shifting this small control group of 12 patients from corn oil to viosterol. In our 1934 study we observed 14 patients throughout the ragweed season who were given a placebo of corn oil alone. Ten of these had asthma in addition to hay fever. Two of the 14 patients reported definite relief of symptoms. One of these reported about 50 per cent relief from both hay fever and asthma. The other reported a similar degree of relief from hay fever. The remaining 12 (85.7 per cent) either were unimproved or were worse than in previous years. Compared with this group were 15 patients who received viosterol alone during the same period. Nine of these had pollen asthma in addition to the hay fever. Eleven of these 15 showed definite relief from allergic symptoms. Eight of the 11 had seasonal asthma in addition to hay fever. Four of the 15 (26.6 per cent) experienced no relief.

The reason for using such a small number of patients for this additional control group was that our interest in the clinical results in these later studies was only incidental. Our primary interest, and this will be the object of this report, was in a study of the blood chemistry with particular reference to calcium and potassium before, during, and after the hay fever season, in treated and untreated patients.

In the small series of 1932 the blood studies were not particularly illuminating. In the series of 1933 a large number of blood constituents was studied serially, in some instances beginning as early as April and following through to November. The factors studied were selected either because of known relationship to vitamin D function or because of suspected or suggested relation to allergic conditions. The list included calcium, inorganic phosphorus, potassium, hydrogen ion concentration, carbon dioxide (total and combining power), cholesterol, nonprotein nitrogen, sugar, and total chloride; the potassium calcium ratio was computed and tabulated. In addition a considerable number of subjects were utilized in a study of the influence of the allergic condition and of the treatment on diffusible calcium. While other factors might have been studied profitably, it was found to be impractical to draw any larger samples of blood, especially in view of the frequency of sampling.

None of the subjects were in the hospital continuously, but every effort was made to secure basal conditions for sampling. The patients were selected not only because they were representative of various types of allergic manifestations but also for intelligence and willingness to cooperate. They were instructed to report without having taken any food in the morning of a definite day scheduled in advance. For various reasons not all of them were able to maintain the schedule as originally planned. Before sampling, each one was questioned carefully about the activities of the morning, especially as to whether food or any other substance had been ingested. Because of these precautions we believe the sampling has been done under basal conditions, although

it is not possible to determine certainly what influence the physical activity of traveling to the laboratory may have had.

It would not be practical to reproduce all our data. Hence the tables are constructed in such a way as to give a composite comparison of the findings in the period before the hay fever season and before any treatment was undertaken with the findings at onset, under treatment, and after the termination of treatment.

BLOOD CALCIUM

There is a rather widespread belief that there is likely to be a low concentration of calcium in the blood in hay fever. Most of the reports on this point, however, are based on single determinations on each of a number of patients. As we have already shown[3] this is not a valid method of investigating this point, since the concentration may be

TABLE I

CONCENTRATION OF TOTAL CALCIUM IN THE BLOOD. CALCIUM IN MG. PER 100 C.C. PLASMA

SUBJECT NO.	PRE-SEASONAL PERIOD		ONSET OF SYMPTOMS		UNDER TREATMENT		POST SEASON		PERCENTAGE OF RELIEF
	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	
4	11.62	10.86	12.00	9.81	12.32	10.35	11.49		75
5	11.23	10.21		9.51	None		12.01	11.73	
10	15.00	8.73	19.75	11.22	19.75	11.22	14.16	10.33	75
17	13.32	9.75	13.09	12.85	21.98	11.73		9.31	50
18	13.00	9.02	11.82	11.29	17.98	9.72	15.48	12.89	25
21	13.01	9.45	12.81	10.39	22.30	9.95	11.19	9.82	100
22	12.29	9.81	11.73		11.62	10.05			75
23	12.31	9.66	11.06	10.49	14.23	10.19			50
25	10.93	9.61	11.81	10.04	12.18	10.04			75
26	11.07	9.26	11.63	10.33	13.92	11.43	12.62	10.60	50
27	12.71	9.43	10.95	10.88	14.12	10.71	12.61	11.05	75
30	12.22	9.25	11.39	10.32	12.31				25
31	11.24	9.64	11.63	10.00	15.50	13.08		9.46	90
34	11.98	9.18	11.12		15.34	10.71		10.68	50
37	12.56	9.30	13.06	10.61	(No report after 8/22)				50
38	11.27	10.68	11.66	10.95	15.11	11.62		10.15	50
40	10.99	9.25	11.58	11.55	12.92	10.80			0
42	10.99	9.22	10.00	9.82	17.21	9.92	12.03		50
43	10.87	8.76	10.46		11.67	9.55			50
44	13.14	9.26	11.35		11.67	10.75	12.87		50
45	12.71	8.91	10.62	9.32	12.11	11.75	No final report		75
48	10.44	9.62	10.86	9.73	15.46	10.08	11.16		50
49	11.11	10.33	10.15	9.95	14.38	9.84	10.94	9.65	75
50	13.06	10.01	13.09	11.99	16.10	11.43	11.66		50
51	11.61	10.48	10.91		12.75	10.87		9.65	75
55	11.33	10.44	10.78	8.65	18.62	10.44	10.31		25
59	10.56	9.99	11.26	10.85	22.36	10.90		9.88	75
61	10.19		11.52	8.65	12.94	10.99		9.65	0
66	12.08	10.15	10.27	8.84	11.91	9.01	10.34		75
76	10.61	8.72	10.20		15.92	10.86	11.35		100
77			12.23	9.12	15.92	11.44	10.32		25
78		10.20	13.33	10.79	17.18	11.37	10.79		0
80	11.08	10.76	11.21	10.61	13.79	10.11	10.05		50
Averages	11.78	9.68	11.42	10.31	15.31	10.70	12.31	10.35	
Grand Averages	10.73		10.86		13.00		11.33		

markedly altered spontaneously within relatively short periods in the same subject. Consequently, even under identical conditions, it does not follow that the same stage of the process of calcium transportation exists in two or more different subjects.

In Table I are shown the findings on the concentration of total calcium in the blood. In the first double column are shown the highest and lowest figures obtained during the period before any treatment was begun and well before the hay fever season had begun. In some cases as many as 20 determinations were made during this period. In two of the cases included in the table no determinations were made in this period because the subjects did not report until after the first symptoms had appeared. During the preseasonal period, before any viosterol was given, the following variations are noted. The highest figure for any one subject was 15.0 mg. of calcium per 100 c.c. of heparinized plasma, the lowest 8.72 mg.; the average for the subject showing the highest figure (No. 10) was 11.59 mg., the average of all of the high figures was 11.78 mg. The average of all the low figures during this period was 9.68 mg., the grand average 10.73 mg.

In the second double column are shown the highest and lowest figures found during the period between the second day before the onset of the first definite symptoms and the fifth day thereafter. The significance of these figures is lessened somewhat by the fact that some of the subjects had already had treatment with viosterol for short periods, while most of them had had no treatment. Also, on some cases only one observation was made during this period, in which case the allocation of the figure in the high or low column was made somewhat arbitrarily. It is of interest that the highest figure (19.75 mg.) again was found for No. 10. The lowest figure in the group was 8.65. The average of the high column was 11.42 mg., that of the low column 10.31 mg., the grand average 10.86 mg. of calcium per 100 c.c. of heparinized plasma.

In the third double column are shown the highest and lowest figures obtained at any time during the period of viosterol administration regardless of the clinical condition of the subjects at the time. The highest concentration of blood calcium found was 22.36 mg., the lowest 9.01 mg. The averages for the respective columns were 15.31 mg. and 10.70 mg., the grand average 13.00 mg.

The clinical histories show that the severity of the allergic symptoms was in all instances quite as great when the high concentrations were found as when correlated with low concentrations. When the higher concentrations are correlated with the percentage of relief shown in the last column—which was explained in an earlier paper[2]—as shown in Table II, there appears to be little reason for ascribing the degree of relief to the change in total concentration of blood calcium.

In the last double column are shown the concentrations found after the termination of the hay fever season and from two to three weeks

after treatment had been discontinued. In most instances these were obtained in the latter part of October and in November. The highest concentration, 15.48 mg., was found on September 28 (No. 18), only

TABLE II

RELATION OF DEGREE OF RELIEF AND TOTAL BLOOD CALCIUM CONCENTRATION. CALCIUM IN MG. PER 100 C.C. OF PLASMA

PERCENTAGE OF RELIEF	PRESEASON		ONSET		UNDER TREATMENT		POST SEASON	
	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW
100	13.01	9.45	12.81	10.39	22.30	10.86	11.35	9.82
	10.61	8.72	10.20	10.20	15.92	9.95	11.19	
Average	11.81	9.09	11.50	10.30	19.11	10.40	11.27	9.82
90	11.24	9.64	11.63	10.00	15.50	13.08		
75	13.70	10.86	19.75	11.73	22.36	11.75	15.48	12.89
	13.00	10.76	12.00	11.24	19.75	11.22	14.16	11.05
	12.71	10.48	11.82	11.22	17.98	10.90	12.61	10.33
	12.71	10.33	11.81	11.12	14.38	10.87	11.49	9.88
	12.29	10.15	11.73	10.88	14.12	10.71	10.94	9.65
	12.08	9.99	11.26	10.85	12.75	10.35	10.34	9.65
	11.62	9.81	10.95	10.04	12.32	10.05		
	11.61	9.62	10.91	9.95	12.18	10.04		
	11.11	9.61	10.62	9.81	12.11	9.84		
	10.93	9.43	10.27	9.32	11.91	9.72		
	10.56	9.08	10.15	8.84	11.62	9.01		
		8.91						
		8.73						
Average	12.03	9.83	11.93	11.45	14.68	10.45	12.50	10.57
50	13.32	10.76	13.09	12.85	21.98	11.73	12.87	10.68
	13.14	10.68	13.09	11.99	17.21	11.62	12.62	10.60
	13.06	10.01	12.18	11.05	16.33	11.43	12.03	10.15
	12.56	9.75	11.66	10.95	16.10	11.43	11.66	9.31
	12.31	9.66	11.63	10.61	15.46	10.75	11.16	
	11.98	9.62	11.35	10.49	15.34	10.71	10.68	
	11.27	9.30	11.21	10.46	15.11	10.19	10.15	
	11.08	9.26	11.12	10.33	13.92	10.11	10.05	
	11.07	9.26	10.86	9.82	13.79	10.08		
	10.99	9.22	10.46	9.73	11.67	9.92		
	10.87	9.18	10.00		11.67	9.55		
	10.44	8.26						
	10.19							
Average	11.71	9.58	11.51	10.86	15.51	10.68	11.53	10.18
25	12.22	10.44	12.23	10.32	18.62	11.44	10.31	
	11.33	9.25	11.39	9.12	15.92	10.44	10.31	
			10.78	8.65	12.31			
				8.65				
Average	11.77	9.85	11.47	9.19	15.62	10.94	10.31	
0	10.99	10.20	13.33	11.55	17.18	11.37	10.79	9.65
	10.19	9.25	11.58	10.79	12.94	10.99		
			11.52		12.92	10.80		
Average	10.59	9.73	12.14	11.17	14.35	11.05	10.79	9.65

ten days after discontinuance of the treatment with viosterol, so it is probably not a basal figure since it usually requires a somewhat longer time for recovery from a hypercalcemia of the degree induced in this case (17.98 mg.). The averages compare well with those obtained in the preseasonal period.

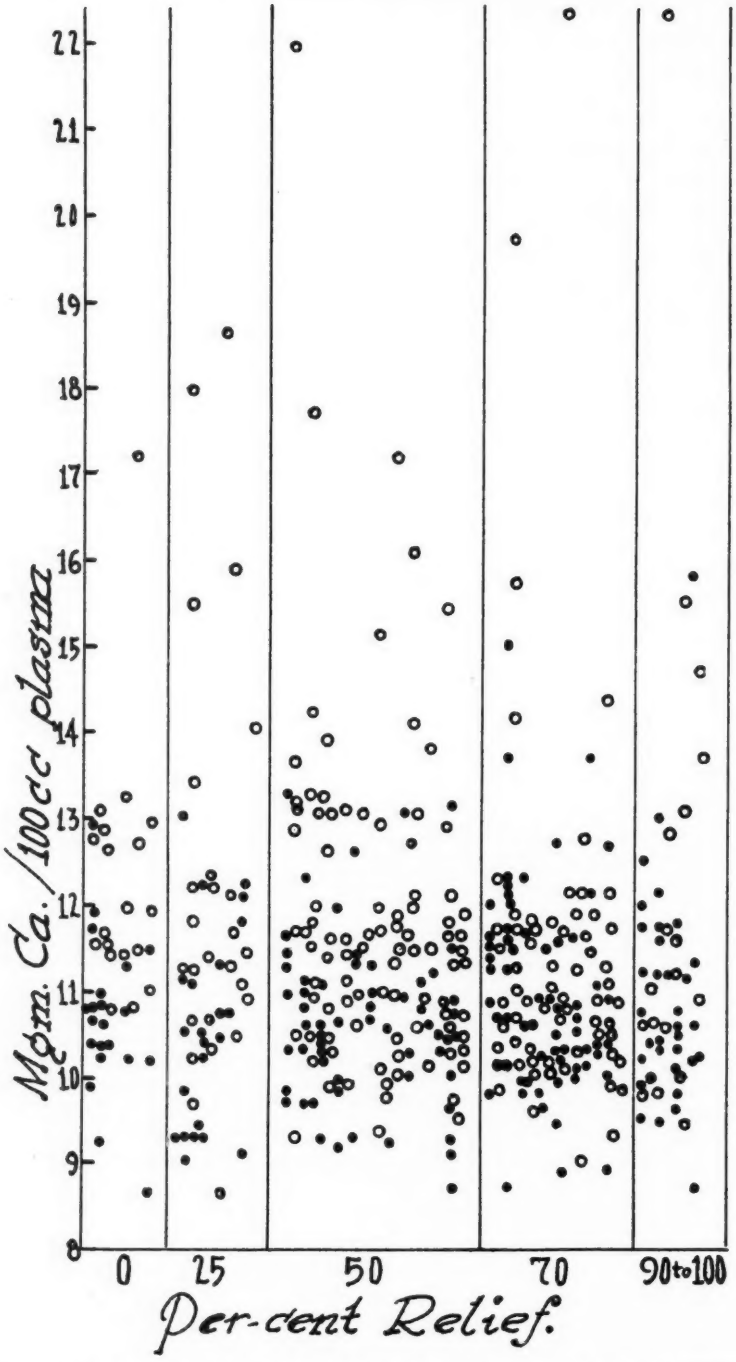

Fig. 1.—Data representing the blood calcium concentrations obtained before treatment. Circles represent those obtained during the period of treatment. The subjects are distributed serially according to the degree of relief. Progression along the abscissa is therefore of no significance except from group to group.

In Fig. 1 is shown the distribution of the figures for blood calcium according to the degree of relief. It is apparent at a glance that in all the groups the spread of both the pretreatment figures and those under treatment is practically homogeneous.

In Table II the same figures are averaged in groups according to the clinical results as indicated by the percentage of relief. The averages in all these groups are comparable for the preseasonal period, for the onset and for the post season. The average of the two cases showing 100 per cent relief is definitely higher during the treatment period than any of the other groups during the same period. For each of the other groups the averages during any of the periods are comparable. Also it will be noted that the highest figures in each group are comparable. Had there been a larger number of patients who had 100 per cent relief, it is probable that this average would have been lower also.

TABLE III

VARIABILITY IN THE CONCENTRATION OF CALCIUM IN THE BLOOD. CALCIUM IN MG. PER 100 C.C. PLASMA

NO. 10 MALE 75 PER CENT RELIEF		NO. 31 FEMALE 90 PER CENT RELIEF		NO. 26 FEMALE 50 PER CENT RELIEF	
5/ 4/33	12.23	6/12	9.64	6/ 5	10.49
5/ 8	11.59	6/16	9.78	6/ 8	10.21
5/11	8.73	6/20	10.51	Menses	
5/15	15.00	6/27	11.24	6/12	9.26
5/18	13.70	7/ 7	Menses	6/15	10.58
5/22	12.16	7/11	10.61	6/22	10.29
5/25	11.37	7/14	10.09	6/30	10.40
		(Treatment begun)			
5/29	10.14	7/21	11.78	7/ 6	11.07
6/ 5	12.33	7/28	10.34	(Treatment begun)	
6/ 8	10.70	7/29	Menses	7/20	9.88
6/12	10.75	8/11	10.83	7/27	Lost
6/15	11.24	8/15	Onset	Menses	
6/22	10.16	8/18	11.63	8/ 4	10.43
6/29	11.73	8/25	10.00	8/11	10.33
				(Onset of symptoms)	
7/ 6	12.05	8/29	Menses	8/18	11.63
Treatment begun		9/ 7	13.08	8/25	13.11
7/20	10.82	9/15	15.50	9/ 1	13.16
7/27	Lost	10/21	9.46	9/ 8	11.43
(Onset of symptoms)				9/15	13.27
8/ 3	19.75			9/22	13.92
8/10	11.76			9/29	13.31
8/17	Lost			10/13	12.62
8/24	11.93			10/20	10.68
8/31	11.22			11/ 3	10.60
9/14	15.74			Still under treatment for arthritis	

As an example of the variability in the concentration in the blood, Table III is composed of the concentrations of calcium obtained in several individual cases during the entire period of observation. No. 10 had 75 per cent relief but did not show a high continuous calcium level, although he did show the highest individual determination both before and after viosterol was given. The spontaneous variations in the total

blood calcium found at different times in this patient before the season and before any viosterol was given emphasize the danger of drawing conclusions from a single determination in any group of patients.

In case of No. 31 there was much less variation at any time and certainly no hypocalcemia at the time of onset of symptoms. The highest concentration (13.08 mg.) was found on September 7, after practically all symptoms of hay fever had disappeared.

TABLE IV

POTASSIUM CONTENT OF THE BLOOD. POTASSIUM IN MG. PER 100 C.C. PLASMA

SUBJECT	PRESEASON		ONSET		TREATMENT		POSTSEASON		PERCENTAGE
	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	OF RELIEF
4	18.32	10.82	11.63	13.61	32.00	11.35		13.06	75
5	17.02	13.61	8.60	5.80	None		13.39	6.88	
10	25.60	10.65	17.78	10.44	17.78	9.14	13.28		50
17	30.19	10.00	21.18		21.18	10.12	26.67		50
18	30.19	10.43		10.32	22.38	9.36	23.03	10.16	75
21	37.28	7.83	15.84	8.51	20.45	10.39	20.77	9.41	100
22	23.36	8.56		9.67	23.52	8.53			50
23	29.94	12.16	16.67		34.43	10.19			50
25	18.40	12.11	18.14	8.44	20.51	8.42			75
26	22.38	10.29	22.86	15.02	27.82	9.38	23.70	13.97	50
27	21.87	8.86		8.56	24.08	8.56		11.94	75
30	23.52	8.51	13.73	10.82	22.14	8.31			25
31	25.70	7.63	15.02	13.06	17.58	13.06		12.31	90
34	33.33	10.66	17.30	8.53	17.30	8.53	15.94		75
37	20.13	14.81	22.06	10.29					50
38	27.34	9.17	12.26	11.15	16.75	7.65	14.42		75
40	18.08	7.84	12.83	8.56	24.42	9.04			0
42	20.13	7.84	19.63		22.69	8.91	15.62		50
43	16.50	6.70	15.84	10.34	18.70	9.88			50
44	18.33	5.80	22.54	7.84	23.36	7.84	17.39		50
45	14.88	10.26	17.39	10.53	17.39	9.94	No final report		75
48	20.64	8.02	21.18	8.89	21.06	9.28	27.82		75
49	13.06	6.61	14.55	9.52	21.62	9.52		12.50	75
50	17.39	8.27	22.38	8.36	22.38	7.68	15.53	13.06	50
51	19.40	9.41	17.39	7.75	20.64	5.46		10.43	75
55	12.40	8.03	13.28	8.86	24.80	8.86	15.69		25
59	18.32	12.31	15.09	12.83	20.77	8.53		12.36	75
61	14.42		16.91	9.41	22.06	8.55		13.61	0
66	26.24	7.98	14.35		19.05	7.02	15.02		50
76	16.00	14.81		10.32	11.27	7.65	17.58		100
77			20.55	10.46	16.00	9.47		13.39	25
78		11.04	12.45	8.44	18.93	9.28	15.94		0
80	16.41	12.11	13.17	11.39	20.00	9.67	15.76		
Average	21.49	9.78	16.81	10.25	21.71	8.69	18.09	12.08	

The third case maintained the highest continuous level of the three cases during the period of treatment but showed the least degree of relief. This case was complicated by arthritis, as described in another paper.[4] The results shown in this table are typical of all the other cases reported.

From these findings it is apparent that there is no consistent deficiency of calcium manifested in the total concentration in the blood. There is no sustained hypocalcemia in the more susceptible subjects as compared with those less susceptible, nor is there any evidence of hypocalcemia constantly associated with the onset of allergic symptoms. Furthermore,

there is no evidence of chronic hypocalcemia during the preseasonal period. The variations noted are within normal ranges.

Still further there is no evidence that the beneficial results of the treatment are directly associated with the development of hypercalcemia. It is true that many subjects did show briefly a pronounced hypercal-

TABLE V

BLOOD POTASSIUM RELATED TO DEGREE OF RELIEF OF SYMPTOMS. POTASSIUM IN MG. PER 100 C.C. PLASMA

PERCENTAGE OF RELIEF	PRESEASON		ONSET		UNDER TREATMENT		POSTSEASON	
	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW
100	37.28	14.81	15.84	10.32	20.45	10.86	20.77	
	16.00	7.83		8.51	11.27	7.65	17.58	
Average	26.64	11.32	15.84	9.44	15.86	9.26	19.17	
90	25.20	7.63	15.02	13.06	17.58	13.06		
Average	25.20	7.63	15.02	13.06	17.58	13.06		
75	33.33	12.31	21.18	13.61	32.00	11.35	27.82	
	30.19	12.11	18.14	12.83	24.08	9.94	23.03	
	27.34	12.11	17.39	11.39	22.38	9.67	15.76	
	21.87	10.82	17.39	11.15	21.62	9.52	15.76	
	20.64	10.66	17.30	10.53	21.06	9.36	14.42	
	19.40	10.43	16.63	10.32	20.77	9.28		
	18.40	10.26	15.09	9.52	20.64	8.56		
	18.32	9.41	14.55	8.89	20.51	8.53		
	18.32	9.17	13.17	8.56	20.00	8.53		
	16.41	8.86	12.26	8.53	17.39	8.42		
	13.06	8.02		8.44	17.30	7.65		
		6.61		7.75	16.75	5.46		
Average	21.57	10.06	16.31	10.13	21.21	8.86	19.39	
50	30.19	14.81	22.86	15.02	34.43	10.19	26.67	
	29.94	12.16	22.54	10.49	27.82	10.12	23.30	
	26.24	10.65	22.38	10.34	23.52	9.88	17.39	
	25.60	10.29	22.06	10.29	23.36	9.38	15.62	
	23.36	10.00	21.18	9.65	22.69	9.14	15.53	
	22.38	8.56	19.63	8.36	22.38	8.91	15.02	
	20.13	8.27	17.78	7.84	21.18	8.53	13.28	
	18.33	7.98	16.67		19.05	7.84		
	17.39	7.84	15.84		18.70	7.68		
	16.50	6.70	14.35		17.78	7.02		
		5.80						
Average	23.00	9.37	19.53	10.28	23.19	8.87	18.11	
25	23.52	8.51	20.55	10.82	24.80	9.47	15.69	
	12.40	8.03	13.73	10.46	22.14	8.86		
			13.78	8.86	16.00	8.31		
Average	17.96	8.27	15.85	10.05	20.95	8.88	15.69	
0	18.08	11.04	16.91	9.41	24.42	9.28	15.94	
	14.42	7.84	12.83	8.56	22.06	9.04		
			12.45	8.44	18.93	8.55		
Average	16.25	9.44	14.06	8.80	21.80	8.96	15.94	

cemia during the period of treatment, but in most instances this was not sustained, nor were symptoms consistently less severe with hypercalcemia. At best hypercalcemia may be an indication of the effects of vitamin D on calcium metabolism, but there is no evidence that hypercalcemia is a necessary accompaniment of the still unknown effects that result in relative protection against allergic reactions by this treatment.

It would be impossible to stress too strongly the importance of recognizing the spontaneous changes in the concentration of calcium. While these do doubtless have some physiologic significance, it is becoming more evident that the concentration of calcium in the blood is *not* fixed and invariable and that the level at any given moment represents the balance between the calcium entering and leaving the blood stream. For this reason the diagnostic significance of the total calcium concentration may be minimized. A sustained low or high concentration may be of great importance, but single determinations or widely separated sampling must be interpreted with great caution.

Because of the significance that has been ascribed in recent years to the relationship of calcium to potassium in the blood, it seemed important to determine the concentration of the latter as well as the potassium calcium ratio.

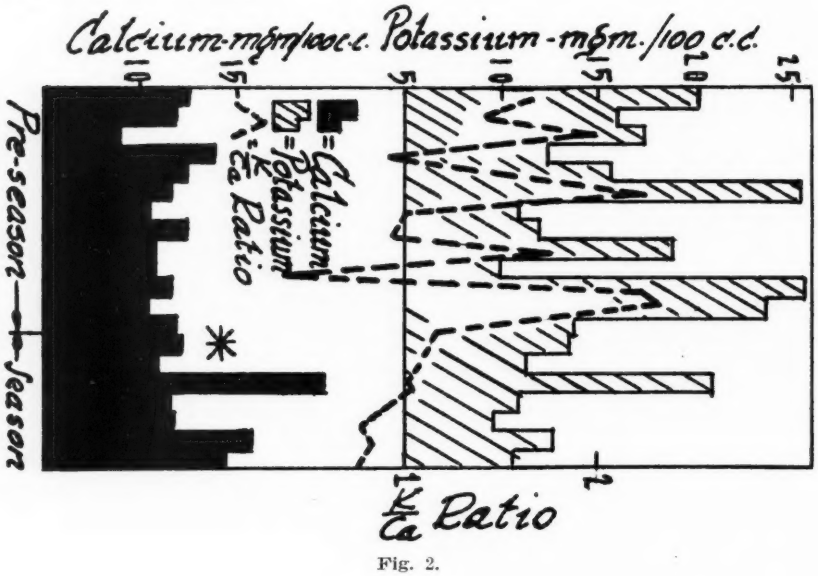

Fig. 2.

The results of the determination of the potassium content of the blood made by the method of Breh and Gaebler[5] are shown in Table IV, arranged as those for calcium in Table I. The highest figure found in any one case in the preseason period was 37.28 mg. per 100 c.c., the lowest 5.80 mg. The average for the high figures in this period was 21.49 mg., for the low figures 9.78 mg. The average for the high at onset was only 16.81 mg., a significant reduction. Because of the greater mobility of potassium as indicated by the wide range of normal variations, it is much more difficult to evaluate the results.

In Table V the results for potassium are arranged in groups, again according to the index of relief. In general, the averages of the high figures show an appreciable reduction at onset as compared with the preseason. A continuous graph of potassium concentrations, however,

does show less fluctuation during the period of treatment in those cases that responded best to the treatment with viosterol (Fig. 2).

Under treatment with viosterol the lower averages are found in the small number who responded best to the treatment. However, the general average for the treatment period in Table IV is practically identical with that for the preseason period.

When the potassium calcium ratio was determined for the group treated in 1933, it appeared that this ratio was reduced as the period

TABLE VI

AVERAGES OF POTASSIUM CALCIUM RATIOS FOR PRESEASONAL PERIOD AND FOR SEASON

SUBJECT NO.	PRESEASON	SEASON	PERCENTAGE RELIEF FROM TREATMENT
4	1.41	1.12	75
10	1.46	0.87	75
17	1.54	1.18	50
18	1.67	1.03	25
21	1.6	1.1	100
22	1.57	1.22	75
23	2.3	1.31	50
25	1.41	1.08	75
26	1.59	1.35	50
27	1.34	1.34	75
30	1.3	1.15	25
31	1.9	1.15	90
34	1.84	1.01	50
37	1.6	1.3	50
38	1.7	1.1	50
40	1.26	1.28	0
42	1.43	1.37	50
43	1.08	1.34	50
44	1.17	1.24	50
45	1.2	1.1	75
48	1.5	1.21	50
49	1.17	1.48	75
50	1.2	0.82	50
51	1.5	1.06	75
55	1.0	1.26	25
59	1.3	0.81	75
61	1.5	1.14	0
66	1.3	1.19	75
76	1.41	0.81	100
77	1.55	0.89	25
78	1.11	0.95	0
80	1.28	1.17	50
Average	1.44	1.14	

of treatment progressed (Fig. 2). But when the averages of all the ratios are computed for the pretreatment period and during treatment (Table VI) it is seen that in only 24 was there a significant reduction in the average potassium calcium ratio during treatment. A composite average also shows some reduction under treatment. This effect on the potassium calcium ratio, however, should not be interpreted as diagnostic, but rather as indicative of a possible trend.

Since it was clearly demonstrated that when serial determinations were made over relatively long periods, there was absolutely no rela-

tionship among the allergic symptoms, the treatment, and the concentrations of the other constituents of the blood that were studied, our further attention during the season of 1934 was directed to a study of the interrelations of calcium and potassium.

Sixty-two cases were selected for blood studies and divided into four groups. One group, hereafter designated UV, was given treatment with concentrated viosterol as described in our earlier papers; a second group, designated UC, received only a placebo of corn oil; a third group, PV, received pollen injections plus viosterol; a fourth group, PC, received pollen injections plus corn oil. Of the total, 20 failed to report regularly or dropped out entirely so that their records could not be included. After all necessary eliminations were made, the numbers in each group were as follows: UV, 8; UC, 8; PV, 17; PC, 9.

The clinical results were in accord with those for the 1933 season, as previously stated. However, a careful statistical analysis of the data obtained from analyses for blood calcium and potassium and calculations of the potassium calcium ratios did not confirm our findings for the 1933 season with regard to changes in the ratio when under treatment.

TABLE VII

	PRESEASON	SEASON
No analyses	255	370
Range mgm. potassium per 100 c.c. plasma	7.60-37.65	4.40-37.28
Mean	17.25	14.00
Standard deviation	5.23	4.44

In Table VII are shown the results of determinations of the concentrations of potassium in the blood of patients observed during the season of 1934. There were 255 analyses before the season and 370 during the season. The ranges of concentration were comparable in the two periods, but the mean was definitely lower in the seasonal period. It is generally accepted by statisticians, however, that unless the difference between the means of two series of numbers is at least three times as great as the standard deviation of the control series, the difference is not of positive significance. It is obvious that this requirement is not fulfilled in Table VII, since the standard deviations of the two series are of the same order and both exceed the mean difference. Therefore, the potassium concentration of the blood did not vary significantly in relation to the clinical condition of the subjects.

Composite graphs of the potassium calcium ratios for each of the groups through the entire period of observation confirmed our previous findings that the ratio was less stable and was higher in the preseasonal period than during the season, but the four graphs, including those individuals who received only corn oil, showed practically identical changes (Fig. 3).

The groups receiving pollen injections alone, viosterol alone, pollen and viosterol, as well as those taking only corn oil as placebo, showed

the same response in the potassium calcium ratio during the season. Before the onset of symptoms the potassium calcium ratio showed no synchronous variations in the four groups. With the onset of the hay

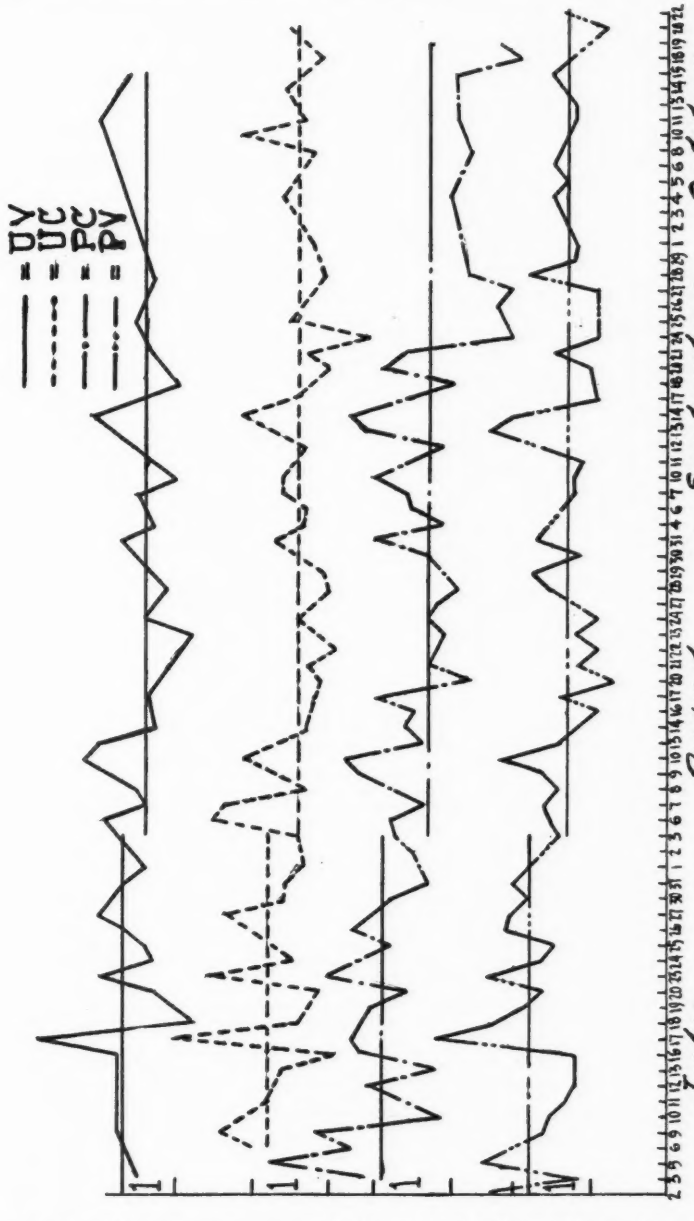

Fig. 3.—Potassium calcium ratio, season of 1934.

fever season, there was a general decrease in the ratio and a diminution in the wide fluctuations of the values during the season as compared with the preseasonal period in all four groups. In our earlier work this observation led us to believe that a leveling off and a decrease in the potassium calcium ratio was a characteristic of effective control of

symptoms of hay fever. A more careful check, however, indicates that it is a finding present in untreated cases, in successfully treated and unsuccessfully treated patients. It was present in those treated with pollen alone, in those treated with viosterol alone, and in those treated with both. It is difficult to say whether this is a characteristic attributable to the allergic state which treatment, no matter how successful, fails to modify, or whether it may be due to seasonal and meteorologic influences as brought out by the work of Petersen and his colleagues.[6]

When the clinical condition of each subject was correlated with the potassium calcium ratio, it was found that during the hay fever season, allergic symptoms, if present, were more pronounced when the potassium calcium ratio was high; or if symptoms were absent they were more likely to become manifest with the occurrence of a rise in the potassium calcium ratio. This correlation, however, was by no means constant and can be considered only generally true.

A composite graph of potassium calcium ratios made for a group of eight normal subjects showed fluctuations of similar magnitude and

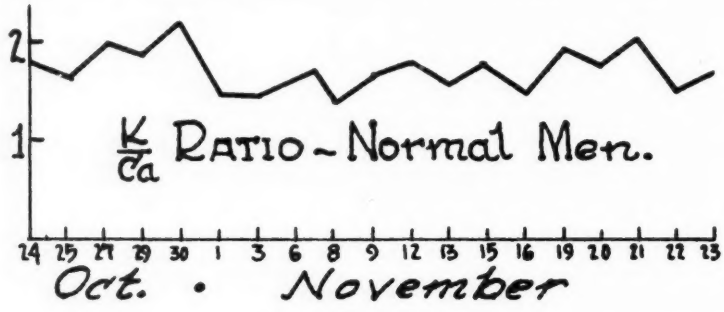

Fig. 4.

frequency over a period of six weeks (Fig. 4). Disregarding for the present any further reference to treatment, since this will be discussed in another paper, a statistical analysis of the potassium calcium ratio for 1934 is presented in Table VIII for groups UC (hay fever patients receiving only corn oil), and PC (hay fever patients receiving pollen treatment and corn oil).

TABLE VIII

STATISTICAL ANALYSIS OF POTASSIUM CALCIUM RATIOS IN THE FOUR GROUPS IN 1934

	PRESEASON		SEASON	
GROUP	NO.	MEAN S.D.	NO.	MEAN S.D.
UC	25	1.89 ± 0.975	87	1.42 ± 0.456
PC	35	2.04 ± 0.565	94	1.46 ± 0.536
UV	27	1.76 ± 0.761	80	1.45 ± 0.411
PV	63	1.76 ± 0.632	175	1.27 ± 0.487

In the group receiving only corn oil (UC), there were 25 observations before the season with a mean ratio of 1.89 ± 0.975; during the

season there were 87 observations with a mean ratio of 1.42 ± 0.456 (Table VIII). According to Fisher,[7] this relationship would allow 66 chances out of 100 that the difference is a random one or without functional significance.

In the group receiving pollen and corn oil (PC) there were 35 preseasonal observations with a mean of 2.04 ± 0.565 and 94 observations in the season with a mean of 1.46 ± 0.536 and a probability of 45, i.e., 45 chances out of 100 that the difference is random (Table VIII). In neither case can we, therefore, attach any significance to the differences observed between the means before the season and those during the season, in relation to the absence or presence of symptoms of allergy. However, a lower potassium calcium ratio was found in both groups during the season when symptoms were present as compared with the ratio before the season. It cannot, therefore, be claimed that either a relative or an actual hypocalcemia is a cause of allergic symptoms. If allergic symptoms were due either to an actual calcium deficiency or to a relative deficiency because of a high potassium concentration in the blood, the potassium calcium ratio should show a rise during the season, especially in the untreated hay fever patients (Group UC).

TABLE IX

POTASSIUM CALCIUM RATIO DURING THE HAY FEVER SEASON COMPARED IN THE VARIOUS GROUPS

GROUP	NO.	MEAN RATIO	GROUP	NO.	MEAN RATIO	PROBABILITY
UC	87	1.42 ± 0.456	UV	80	1.45 ± 0.411	92
UC	87	1.42 ± 0.456	PC	94	1.46 ± 0.536	95
UC	87	1.42 ± 0.456	PV	175	1.27 ± 0.487	66
UV	80	1.45 ± 0.411	PV	175	1.27 ± 0.487	78
PC	94	1.46 ± 0.536	PV	175	1.27 ± 0.487	79
PC	94	1.46 ± 0.536	UV	80	1.45 ± 0.411	98

In the third group (UV, receiving only viosterol), there were 27 preseasonal determinations of the potassium calcium ratio with a mean of 1.76 ± 0.761 and 80 during the season with a mean of 1.45 ± 0.411, with a probability of 72. In the fourth group (PV, receiving both pollen and viosterol), there were 63 preseasonal determinations with a mean of 1.76 ± 0.632 and 175 during the season with a mean of 1.27 ± 0.487 and a probability of 54. In Table IX a similar statistical comparison is made between the results in the season for each of the treated groups (UV and PV) with the corresponding control group. In all cases the probabilities are so high that one may accept at once the conclusion that the differences between the mean ratios for the groups is not of functional significance.

Thus it appears that the changes in the blood constituents studied are not related to the presence or severity of allergic symptoms, nor to the treatment with vitamin D.

ULTRAFILTRABLE CALCIUM

The next point of interest, then, is the possibility of a relationship between the treatment and the state of blood calcium as manifested by its diffusibility. The diffusible calcium was determined by the method of Ingraham, Lombard and Visscher,[8] the essential feature of which is the control of the hydrogen ion concentration in the ultrafilter to a constant at 7.4. It had previously been reported by Greenberg and Gunther,[9] who used their own method in which the hydrogen ion concentration was not controlled, that total and diffusible calcium vary within normal ranges in allergic conditions.

We were able to make determinations of ultrafiltrable calcium in 13 subjects. The most complete of these was made on a young man with uncomplicated hay fever of both vernal and autumnal types which had recurred for six years previously. Since the study was continued from April 12 to November 22, it would occupy too much space to reproduce all of the figures here; consequently Table X shows the average results

TABLE X

AN ADULT MALE SUBJECT WITH VERNAL AND AUTUMNAL UNCOMPLICATED HAY FEVER CALCIUM IN MM/KG. PH 20 IN PLASMA. AVERAGES FOR PERIOD AS DESCRIBED IN TEXT

PERIOD	TOTAL CA	UF CA	TREATMENT	SYMPTOMS
1 (4/12- 5/ 1)	3.11 ± 0.028	1.65	0	0
2 (5/ 2- 7/ 5)	3.01 ± 0.45	1.52 ± 0.518	Vitamin D	3 definite attacks of hay fever
3 (7/ 6- 7/30)	3.12 ± 0.49	1.79 ± 0.32	Vitamin D	0
4 (7/31- 9/ 5)	2.95 ± 0.024	1.78 ± 0.012	Vitamin D	Mild but constant
5 (9/ 6-10/ 1)	3.24 ± 0.349	1.77 ± 0.078	Vitamin D	0
6 (10/ 2-10/30)	3.10 ± 0.179	1.80 ± 0.182	0	0
7 (10/30-11/ 7)	2.68 ± 0.375	1.69 ± 0.015	Vitamin D	0
(11/ 8-11/15)	2.65	1.25	0	0
(11/15-11/22)	3.92	1.94	Vitamin D	0

for certain well-defined periods: (1) April 12 through May 1, before allergic symptoms had appeared and before any treatment; (2) May 2 through July 5, which covers a period of treatment in which three definite attacks of hay fever of a fulminant type occurred. The total vitamin D consumed during this period was 3,300,000 units. (3) July 6 through July 30, when no symptoms of hay fever were present; a total of 2,800,000 units of vitamin D were administered in this period. (4) July 31 through September 5, when very mild symptoms of hay fever were present practically continuously; a total of 6,900,000 units of vitamin D were ingested. (5) September 6 through October 2, when no allergic symptoms were present but a total of 6,900,000 units of vitamin D were given. (6) October 2 to October 30, when no allergic symptoms were present and no treatment was administered.

In the first period there were six determinations of total calcium but only one of ultrafiltrable calcium. Beginning on May 2 the subject received daily 15,000 units of vitamin D up to May 30, and thereafter 60,000 units daily to July 6. There were three definite but mild attacks

of hay fever lasting only through one day each. In all three the total calcium was reduced slightly to 2.85, 2.31 and 2.39 mM, respectively, but these figures are still within the normal range. The ultrafiltrable calcium was 0.91, 0.89 and 1.27 mM, respectively. The first two are definitely below the normal ranges found in any of our determinations on normal subjects. It is possible that the fulminant type of attack may be associated with these changes. In the "3" period there were no allergic symptoms, while in the "4" period mild symptoms were constantly present, yet there were no significant differences between the means for either the total or the ultrafiltrable calcium. In neither period do the mean differences exceed greatly the standard deviations. The same is true when these periods are compared with the "5" and "6" periods. Hence neither the symptoms of allergy nor the administration of vitamin D in large doses is associated with any significant changes in the total concentration or the state of blood calcium.

Beginning on October 30, this subject received daily 600,000 units of vitamin D through November 7. The means for this period were 2.68 $\pm$ 0.375 and 1.69 $\pm$ 0.015 mM respectively. After a rest of a week the figures were 2.65 and 1.75 mM. A dose of 1,000,000 units daily was then administered for a week, after which the concentrations were found to be 3.92 and 1.94 mM. From these findings it appears that the doses administered during the hay fever seasons did not constantly affect the total or ultrafiltrable calcium, although there was marked clinical relief as compared with previous seasons. Only after the dose was increased to 1,000,000 units daily was there any significant elevation of the total and ultrafiltrable calcium. Even then the figures were within the ranges previously found.

The results in this case are typical of those found in the other subjects, so that no further data need be presented on this phase of the problem in patients similarly studied.

The variability of response makes it clear that the relation of the state of blood calcium to the attack of asthma or hay fever is a random one, thus confirming Greenberg and Gunther's[9] conclusion that the diffusibility of calcium is not altered in allergic conditions.

This phase of the problem was approached in another way by investigating the ultrafiltrable calcium in eight of the 28 untreated hay fever subjects confined to an air-conditioned room as described by Rappaport, Nelson and Welker.[15] The patients studied were confined in an eight-bed ward which was almost completely pollen free and in which the temperature and humidity were under constant control. In only three of these was it possible to obtain a sample of blood before the season. The detailed data would occupy too much space for reproduction here, but graphs constructed from the figures showed an entirely random variation. There were 17 determinations made before entering the room, 14 while residing in the pollen-free room, 22 during the remainder of the season after leaving the room and being exposed to pollen, and 7

were made late in October well after all symptoms of pollen allergy had disappeared. The means of all figures of the ultrafiltrable calcium for these four periods were 1.88 before admission to the room while most of them were free from symptoms; 1.72 while confined to the pollen-free room; 1.79 after being discharged from this room and while symptoms were present; 1.76 mM per kg. of water at the end of the hay fever season when symptoms had completely subsided. In view of the fact that the extreme range was 1.19 to 2.43, these differences cannot be considered of any significance so far as allergic symptoms are concerned.

It is well recognized that diffusible calcium includes more than the ionized portion, but many interpretations have been made of alterations in diffusible calcium. In most of the determinations by various methods the hydrogen ion concentration in the diffusion system has not been controlled. In this work the hydrogen ion concentration was closely controlled to a constant in all experiments. In spite of this the variations in the results are such that they cannot be correlated with the variables under investigation, i.e., the allergic symptoms. Therefore, the allergic symptoms are not dependent on the concentration of diffusible or ultrafiltrable calcium, nor is the concentration dependent upon the physiologic changes underlying the production of symptoms of allergy, nor upon the treatment alleviating these symptoms.

The introduction of a biologic method of determining ionized calcium by McLean and Hastings[10, 11] has provided a more nearly physiologic criterion for the study of the function of calcium. In regard to the other blood constituents included in this study, there was even less evidence of a significant correlation so that it is not worth while to occupy more space in the presentation of the detailed data.

ACTION OF VITAMIN D

We have no explanation to offer about the nature of the action of vitamin D in protecting allergic subjects against clinical symptoms. While there is no reason to suppose that there is any relation between its action and hyposensitization by pollen injections, there is certainly no antagonism between the two, since the combined administration of both is unquestionably more efficacious than either one alone.

The results are not due to any change in any of the constituents of the blood included in this study. In another project it has been shown that amount of vitamin D above 10,000 units per kilo increase the output of calcium in the urine and may eventually bring about a negative calcium balance which is not, however, constantly associated with hypercalcemia.

That vitamin D, even in large doses, does not act through the parathyroids seems to be fairly well established. That it does stimulate the thyroid is suggested by work in progress in our laboratories, as well as by that of Handovsky.[12] Landelius and Ljungkvist[13] have confirmed

the frequently reported observation that vitamin D restores the metabolic rate to a normal level in rickets. The work of Gelfan[14] suggests the possibility that there is a catalytic effect on peripheral tissues. The exact nature of the therapeutic action of vitamin D in allergy and other clinical conditions will be understood only when the fundamental nature of the action of the vitamin itself is elucidated.

DOSAGE AND TOXICITY

The dose of vitamin D necessary to protect against allergic manifestations varied greatly in different subjects. In no case was any protection noted on a daily dose of less than 200,000 U. S. P. units. In about 50 per cent of cases it was necessary to increase to 500,000 units. In a few cases as high as 1,000,000 units were given; while in still others as high as 2,500,000 to 3,000,000 units daily were given for short periods. In 1933 most of the subjects were placed on treatment from two to four weeks before the beginning of the season. It was found, however, that this was not necessary, and subsequently treatment was begun a week in advance in most cases. The fact that those subjects who did not begin treatment until allergic symptoms were present experienced definite alleviation of the severity of attacks within four to seven days indicates that the vitamin begins to act very promptly.

Quite properly there is much concern over the possibilities of permanent injury resulting from such large doses of vitamin D. This has been discussed at some length previously,[16, 17] but since, additional evidence has been secured that with strict adherence to simple precautions as outlined[4] such doses may be given with as much assurance of safety as with any one of the many therapeutic agents now utilized under similar precautions.

Much misunderstanding has arisen because of the findings in experiments on animals of extensive pathology after heavy administration of vitamin D. A more detailed discussion of this point will be presented in another paper, but it may be said with certainty that in *all* such experiments the dose per kilo of body weight was very greatly in excess of that given to any human subject except in one instance.[18]

For one purpose or another during the past six years, concentrated vitamin D in some form has been administered to more than 700 human subjects including a large number of normal individuals. From observations made on these together with experimental findings on animals, it appears that the first manifestation of toxic effects is destruction of individual tissue cells which may appear in any tissue but are probably more numerous in the kidney. Symptoms of toxicity appear at this time. Calcification does not occur until after this stage and first appears in the sites where cells have been destroyed. At this stage cessation of administration of vitamin D allows these injuries to be repaired, with no deposition of calcium or only a transient deposition that was promptly removed.

Analyses of various tissues for calcium content show that the kidney is likely to be most seriously affected. Consequently any subject displaying kidney pathologic condition should under no circumstances be subjected to this treatment. Also it should be used with extreme caution in older people. It has been given to people at the advanced ages of 74 to 76, but only after careful clinical check.

SUMMARY

1. Since it has been shown that allergic symptoms which develop in pollinosis are not due to changes in the blood calcium or potassium, it is not surprising that the protective action of vitamin D is not correlated in any way with changes in these or any other constituents of the blood.

2. The nature of the protective action of vitamin D in pollinosis cannot be determined from data available at present.

3. Vitamin D in doses large enough to protect against pollen allergy should not be administered to patients with any pathologic condition of the kidney.

4. The protective action of vitamin D either alone or in combination with pollen hyposensitization is not apparent in doses less than 4,000 units per kilogram of body weight in any large number of subjects.

5. The combination of vitamin D and pollen hyposensitization gave measurable protection against the symptoms of allergy in pollinosis in about 90 per cent of all subjects. Complete relief was apparent in approximately 6 per cent of all subjects so treated in the three seasons.

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DISCUSSION

DR. ARMAND COHEN, Louisville.—I should like to ask one question. In the administration of these large doses of viosterol, were any cases of vitamin D toxicosis encountered?

Following the original report by Dr. Rappaport, of the use of these potent doses of viosterol in the treatment of refractive cases of pollinosis, I obtained a liberal supply of this substance from Mead, Johnson & Company.

One of the patients given the doses of viosterol as suggested by Dr. Rappaport, developed a severe dermatitis of the hands. She was seen by a competent dermatologist, who after considerable study diagnosed the condition as hypervitaminosis. Following the withdrawal of the use of the vitamin, the condition cleared up promptly and completely.

Because of the fact that vitamin D is the only vitamin known to have certain potential dangers associated with its use, I have been prompted to call your attention to this one case.

DR. RAPPAPORT.—I did not have the opportunity to take up many questions, including that of toxicity in dosage. I shall not take it up in detail at present. Concentrated viosterol is dangerous in that some people can tolerate only very small doses. We have found that two to nine drops of the material, which amounts to 200 to 900 drops of ordinary D viosterol, are the optimum dose. You rarely have to go above nine drops, and that dose has not proved to be toxic in any case.

One patient I can recall, out of some five or six hundred, was sensitive to corn oil and with two drops had attacks of abdominal pain and diarrhea. The first symptom that occurs from an overdose usually is frequency of urination. Other early symptoms are loss of appetite, abdominal distress, nausea, and vomiting. When these occur, the viosterol is withdrawn. The symptoms subside in two or three days.

As far as animal experimentation work is concerned, one can give as much as 20,000 U.S.P. units per kilogram of body weight with no harm, which is much higher than we gave. We gave some patients as high as 75 drops and 90 drops per day, which is the equivalent of 9,000 drops of 250 D, but that was in our first group of cases when we did not know what optimum dose was, and we expected better effects from large than from small doses. The maximum we gave was only 4,000 U.S.P. units per kilogram of body weight, and in animals you can go as high as 20,000 kilograms of body weight for four months before there are any toxic effects. The first toxic effects in animals are also in the kidney, with injury of the kidney cells, which in early cases is reversible. As far as we know, no damage is done to human beings by limiting the dose to 9 drops of 10,000 viosterol daily.

I believe this problem is of sufficient importance to bear repeating by other workers.

STUDIES ON POLLEN AND POLLEN EXTRACTS*

XIV. The Effects of Varying Hydrogen Ion Concentration Upon the Stability of Pollen Extracts

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Chicago, Ill.

SUCH attempts at hydrogen ion concentration control of pollen extracts as have been made in the past have been directed toward buffering the solution at an alkalinity approximately that of body fluids. No direct comparison has been made of the initial potency and the stability of pollen extracts in various buffer solutions, acid and alkaline, under the same conditions. Stier and Hollister[1] have reported that addition of sodium bicarbonate decreases the antigenic properties of pollen extracts.

The purpose of this study has been to determine whether slight acidity or alkalinity, as produced by buffers, has any effect on the potency and stability of pollen extracts. All other factors have been kept constant so far as possible.

Experiments conducted over three years have demonstrated that pollen extracts in 5 per cent dextrose are as stable as those in the commonly used glycerosaline.[2] The present work has been carried out by comparison of the buffered extracts with an unbuffered extract in dextrose menstruum.

EXPERIMENTAL

The buffer solutions used as extracting fluids were prepared by adding to each 90 c.c. dextrose menstruum, the following buffer solutions[3]:

II. 9.5 c.c. KH_2PO_4 (M/15) and 0.5 c.c. Na_2HPO_4 (M/15)
III. 3.0 c.c. KH_2PO_4 (M/15) and 7.0 c.c. Na_2HPO_4 (M/15)
IV. 0.5 c.c. KH_2PO_4 (M/15) and 9.5 c.c. Na_2HPO_4 (M/15)
V. 6.75 c.c. $NaHCO_3$ (2.7%)
Solution I, unbuffered dextrose menstruum, contained 5 per cent dextrose and 0.5 per cent phenol.

Pollen extracts were prepared by extracting 3 gm. pollen with 100 c.c. of the extracting fluid. Equal parts of short and giant ragweed pollen were used.

*From the Department of Medicine, Northwestern University Medical School, and the Research Department, Abbott Laboratories.

Table I shows the hydrogen ion concentration of the solutions and of the finished extracts prepared from them, as determined by the glass electrode.* The buffering capacity of the pollen itself appears quite remarkable.

TABLE I

SOLUTION NO.	SOLUTION pH	POLLEN EXTRACT pH
I	4.2	6.4
II	5.6	6.1
III	7.1	6.6
IV	7.6	6.7
V	8.3	7.5

The freshly prepared extracts were tested by intradermal comparisons of serial dilutions upon ragweed sensitive patients. Similar extracts were placed in the incubator at 37° C. to speed up any deterioration, and were then compared by the same method after incubation for thirteen months or longer.

For testing, decimal dilutions of the extracts were prepared from 1:1,000 up to 1:1,000,000,000. The proper dilutions were injected intradermally into sensitive patients, taking care to inject the same amount in each case. Because of lack of space, all the solutions could not be compared upon the same patient at the same time, but at each sitting two to four of the buffered extracts were compared with the unbuffered one. The aim was to find the dilution at which the extract just failed to react. The cases in which this goal was not attained, due to improper selection of dilutions for the patient, are not included in the reports. The extract reacting in higher dilution was assumed to be the stronger.

In order to avoid undue length of tables, only the final results are recorded. Table II shows the results of comparative tests of the freshly prepared extracts.

TABLE II

COMPARISON OF BUFFERED EXTRACTS WITH UNBUFFERED (I). FRESHLY PREPARED

	II	III	IV	V
No. of tests stronger than I	1	3	3	2
No. of tests equal to I	13	7	10	12
No. of tests weaker than I	9	13	8	8

The number of tests, as given in Table II, refers to the number of patients upon whom the given buffered extract reacted in higher, equal, or lower dilution than the unbuffered extract.

TABLE III

COMPARISON OF BUFFERED EXTRACTS WITH UNBUFFERED (I). AGED EXTRACTS

	II	III	IV	V
No. of tests stronger than I	7	5	7	14
No. of tests equal to I	9	5	3	4
No. of tests weaker than I	0	5	1	2

*We are indebted to Mr. K. J. Bauer for these determinations.

After the samples had remained in the incubator for thirteen months, dilutions were made and their relative potency was determined by comparative intradermal tests on hay fever patients by the same methods used for the fresh extracts. Later dilutions were made after longer incubation, but in every case all samples had remained in the incubator for the same length of time and are, therefore, comparable. Table III gives a summary of these.

THERAPEUTIC RESULTS

Buffered extracts of the composition of (V) have been used for treatment of hay fever patients for about six months. The buffered and unbuffered extracts were freely interchanged with no clinical difficulty, e.g., reactions. The use of the buffered extract was not attended by pain such as comes with glycerinated extracts. The results of treatment likewise do not seem to differ.

DISCUSSION

While the differences above noted are not marked, it may be stated that freshly prepared pollen extracts in unbuffered isotonic dextrose solution are at least as potent as those prepared in solutions buffered at a point slightly acid or slightly alkaline. There is some evidence that buffering at either slightly acid or alkaline hydrogen ion concentration may increase the stability.

The extract buffered with sodium bicarbonate (V) has the advantage that no glucoside is deposited on standing, as occurs with all the other solutions. The quantity of extract after incubation did not permit a determination of the hydrogen ion concentration, but it probably had become more alkaline than hydrogen ion concentration 7.5, due to loss of carbon dioxide. The color of alkaline extracts is very much deeper than that of unbuffered extracts.

SUMMARY

It has been shown that the presence of buffer salts in dextrose menstruum does not increase the potency of ragweed pollen extracts prepared with such solutions. Ragweed pollen extracts in isotonic dextrose buffered at either a slightly acid (hydrogen ion concentration 6.1) or slightly alkaline (hydrogen ion concentration 7.5) reaction have been shown to be at least as stable as similar unbuffered extracts. There is some indication that such buffering may increase stability. Alkaline buffer is probably to be preferred, as it prevents precipitation of the glucoside and thus prevents the development of a cloudy appearance on standing. Therapeutically, the same results were obtained with the extract buffered with sodium bicarbonate as with a similar unbuffered extract.

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THE EFFECT OF MASSIVE POLLEN THERAPY ON SKIN TEST SENSITIVITY*

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THERE is considerable difference of opinion as to the relationship between specific pollen treatment and its effect on skin test sensitivity. The literature concerns itself chiefly with questions as to whether specific pollen treatment reduces skin test sensitivity; whether clinical relief parallels the reduction of skin tests; and whether it is necessary or advisable to produce such reduction of skin tests.

Colmes[1, 2] in 1932, reported a series of hay fever cases in which scratch tests done before treatment was started, were compared with the tests obtained after the final dosage was reached. In 44 cases he found that under the influence of pollen treatment, 81 per cent showed a diminution in their skin test sensitivity and in an additional 9 per cent they were completely extinguished. The best end-results of pollen therapy were obtained by him in those cases showing marked diminution of skin test sensitivity.

Preceding Colmes's work, Clause,[3] Oppenheim and Gottlieb,[4] Koessler,[5] Kolmer,[6] and Phillips[7] have used the skin tests as a guide to specific treatment, the diminution of skin tests serving as an index to the patient's immunity. Others have used the ophthalmic tests. Vaughan[8] using the ophthalmic test with various dilutions, found that 75 per cent of those who became negative to the 1:20 dilution of pollen received adequate relief. He felt that the skin reaction was not a satisfactory criterion of adequate desensitization. Cooke,[9] however, stated that he found no diminution of the ophthalmic tests during or after treatment. His patients still gave reactions, even though symptomatically free. G. T. Brown,[10, 11, 12] using doses from 100,000 units to 200,000 units, stated that the majority of successfully treated patients will show a marked diminution of skin reactions, and a number will show complete disappearance of previously positive tests. Others who have reported reduction in skin tests after treatment are Goodale, Walker, Cooke, Larson and his associates, and Lamson, Piness, and Miller (quoted by Colmes).

Contrary views, however, as to the effect of pollen therapy on skin sensitivity have been expressed by Markow and Spain.[13, 14] These authors state that in most of their cases showing reduced skin tests after treatment, it could be shown that the reduction was due to deteriora-

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tion of the pollen extract used for testing. Tests done by them with freshly prepared pollen extracts after treatment showed no remarkable changes from those done before treatment. They concluded that treatment with "high doses" of pollen extract does not cause an appreciable reduction in skin tests. They make no statement, however, as to what they consider "high doses" of pollen extract. Levine and Coca[15] concluded from experimental work, that the "skin tests remain unchanged following specific pollen therapy." Rackemann[16] in his textbook states that the "skin tests at the end of treatment are sometimes smaller, are more usually the same, and occasionally larger than at the beginning of treatment." Also that "end-results are not parallel with, or dependent upon, such desensitization as would be indicated by a diminishing of skin reaction." However, more recently, in a report by Colmes,[17] he concluded that good results in treatment were accompanied by a diminution of skin tests in a majority of patients. Yet 18 per cent of the patients had good results without a decrease in skin tests, and 11 per cent had poor results despite a diminution in skin tests.

During the past three years I have attempted to check by scratch tests the skin sensitivity of my treated ragweed hay fever cases and have compared them with the tests performed before treatment was begun. In contradistinction to others, no attempt was made to regulate the size or rate of pollen doses by serial skin tests. The patients were treated in the following manner.

During the 1933 and 1934 seasons, pollen extracts were made by extracting 3 grams of pollen in 100 c.c. of 50 per cent glycerin-Coca solution with 0.5 per cent phenol.

During the 1935 pollen season, extracts were made in 5 per cent glucose, using 0.5 per cent phenol as a preservative. Twenty-four hours of frequent shaking was followed by extraction for one week in the ice box. The pollen solution was then filtered through a Seitz filter. In the case of the glucose extracting fluid it was found that when the extraction was allowed to continue for one week, no precipitate formed after filtration. The nitrogen determinations on these extracts ranged from 0.32 mg. to 0.35 mg. per c.c. This 3 per cent extract is arbitrarily considered as containing 30,000 pollen units per c.c.

The patients were roughly classified as to their degree of sensitivity, by means of the scratch test. Those showing unusually large reactions were placed in the most sensitive group. The majority of cases showed average reactions and were placed in the moderately sensitive group. Those showing negative or slightly positive reactions to the scratch test were placed in the third, or low sensitivity, group. Patients in this latter group are omitted from this report because of poor initial skin reactions.

Treatment was begun in the moderately sensitive group with 3 to 5 pollen units of pollen extract (0.03 to 0.05 c.c. of 1:10,000 dilution).

This dosage was doubled at first, and later increased from 30 per cent to 50 per cent, depending on local reactions. The average dose reached by the beginning of the pollen season in this group, was 2 c.c. of the 3 per cent extract (60,000 pollen units) for adults, and 1 c.c. (30,000 pollen units) for children. In the case of the exquisitely sensitive patients the initial dose was as low as $\frac{1}{50}$ to $\frac{1}{5}$ pollen unit (0.05 to 0.5 c.c. of 1:1,000,000 dilutions). There were three patients in the exquisitely sensitive group whose top dose varied from 4,500 pollen units to 12,000 pollen units (0.15 to 0.4 c.c. of 1:33 dilution). In a few cases of the moderately sensitive group the top dosage reached was as high as 90,000 pollen units (3 c.c. of 1:33 dilution). It generally required from 23 to 30 injections to reach this dose, after which an injection was given at weekly intervals throughout the pollen season, until the end of September, thus bringing up the average number of injections between 30 and 38. It was found that by injecting the extract deeply, always in approximately the same site, in the same arm, the tendency to severe local reactions was considerably reduced. This technic allowed a more rapid increase of dosage. The perennial method was continued in most patients, by giving half the maximum dose every three or four weeks, and raising this to the previous level, prior to the pollen season. Weekly injections were given during the pollen season, as before.

The scratch tests were performed with the instrument described by Lewis Webb Hill.[18] This device produces circular scratches, uniform in size and depth. The tests were made with dry pollen, using tenth normal sodium hydroxide. In testing patients for fall hay fever, the following pollens were routinely used: short and giant ragweed, cocklebur, and wormwood sage. For this report, only the reactions to ragweed will be considered, although patients frequently received in addition to ragweed, one or both of the other pollens, depending on their skin reactions.

TABLE I

EFFECT OF LARGE THERAPEUTIC DOSES OF POLLEN EXTRACT ON SKIN REACTIONS

CASES TREATED	BEFORE TREATMENT	AFTER TREATMENT				
		4 PLUS	3 PLUS	2 PLUS	1 PLUS	NEG.
47	4 plus	0	3	6	29	9
29	3 plus		2	9	15	3
11	2 plus			1	9	1
87		0	5	16	53	13

Four-plus reactions were those which were 15 mm. or larger in size, in their largest diameter. Three-plus reactions were approximately 10 mm. in size. Two-plus reactions were about 5 mm. in size. One-plus reactions were those barely discernible but having definite pseudopods.

Eighty-seven cases of ragweed pollen hay fever with and without asthma are included in this study. These patients were seen during the ragweed pollen seasons of 1933, 1934, and 1935, and were selected be-

cause of definitely positive scratch tests prior to treatment. There were three exquisitely sensitive patients in this group. Cases of pollinosis with slightly positive or negative scratch tests are omitted.

RESULTS

Eighty-four of the 87 patients (96.5 per cent) treated, showed reduction in skin tests. Eighty-one per cent of the four-plus reactors were reduced to one-plus or negative. Of these, 19 per cent were negative. Sixty-one per cent of the initial three-plus reactors were reduced to one-plus or negative. Of these, 10 per cent were negative.

Three patients showed no change in their skin reactions, yet two of these had good results, one having a poor result. Ninety-three per cent of the patients had good results from treatment, there being five failures. These failures were as follows: Two patients in whom the initial skin tests were reduced from four-plus and three-plus, respectively, to one-plus, received as their top dose 60,000 pollen units (2 c.c. 1:33 extract). One patient in the exquisitely sensitive group with marked initial skin reactions showed moderate reduction of the skin tests at the end of treatment. He received 12,000 pollen units (0.4 c.c. 1:33 extract) as the top dose. One patient with initial and final three-plus skin reactions received a top dose of 60,000 pollen units (2 c.c. 1:33 extract), and yet had a poor result. One patient with initial two-plus reaction reduced to one-plus after receiving 60,000 pollen units (2 c.c. 1:33 extract).

It was observed that the larger the initial skin reaction, the greater the reduction after treatment. In 47 cases showing four-plus reactions before treatment, 81 per cent were reduced to one-plus or negative, and 19 per cent were negative. In the group showing initial three-plus reactions, only 61 per cent were reduced to one-plus or negative reactions, and 10 per cent were negative.

There was no patient in whom the skin reaction became negative who failed to obtain a satisfactory result from treatment, although there were in this group a number of patients who occasionally had very mild symptoms during the pollen season.

DISCUSSION

The term "massive pollen therapy" is entirely relative. G. T. Brown, who has been the foremost exponent of "high dosage" therapy, would consider such top doses rather moderate. Other workers have not found it necessary to attain doses approximating even 25 per cent of these amounts. In many of the previous reports on the effect of specific pollen treatment in relationship to reduction of skin tests, the doses were considerably smaller. The reason that such large doses were used in my patients is that the experience of previous years' treatment showed that a considerable number of patients were not getting good relief when

smaller doses were used. In passing, it should be mentioned that complete testing for factors other than pollen had been done routinely only in those patients who showed perennial symptoms, rather than carrying out complete skin tests routinely. In patients previously unsuccessfully treated with smaller doses, it was found that by carrying the dosage to the high levels mentioned above, which is now my practice, the majority of patients have obtained good results.

The divergence of views as to what pollen therapy does to the skin tests seems to depend on how high pollen therapy is carried. It is quite possible that in areas of high pollen concentration such as Detroit, where this work was done, much higher pollen doses are necessary to elevate the patients' tolerance sufficiently to be effective. It is reasonable to assume that in many areas, particularly in the eastern states, in which the pollen concentration in the air is lower, such high doses are not necessary to achieve equally good results. For this reason, workers in that region have not reached such high doses, and have, therefore, not produced in their patients as high a percentage of diminished skin reactions, and yet have obtained good clinical results.

It is generally accepted that the size of skin reactions does not indicate accurately the degree of clinical sensitivity, and the extent of the clinical response to the allergen; but, in the individual patient, reduction in the skin reaction does seem to indicate reduction in clinical sensitivity.

These findings are in accord with those of Chandler Walker,[19] who reported that in those in whom the skin test becomes negative, a great majority are able to carry on for a number of years without additional treatment. He found that in his group of permanently cured hay fever cases 22 per cent showed negative skin reactions, and an additional 22 per cent showed very faint reactions.

Many workers, including G. T. Brown,[11, 12] Spivacke,[20] and Piness and his associates,[21] have felt that the abolition of the skin tests augurs well not only for the seasonal cure but for a more or less permanent one. It is not the intention of this paper to insist that a cure of hay fever necessitates the abolition of positive skin tests. It is merely a report on what has occurred to the skin tests after the use of high doses of pollen extract for treatment.

This study has provided an opportunity also for comparing two extracting fluids, 50 per cent glycerin-Coca solution, and 5 per cent glucose solution with 0.5 per cent phenol. It was found that the clinical results were no different with the two fluids. There was, however, almost a complete absence of pain with large volumes of the glucose solution. The large injections of the glycerin-Coca solution, however, were sometimes very painful and occasionally produced induration. There was no difference in the number of general reactions, which were surprisingly infrequent, there being five in 1933, six in 1934, and eight

in 1935. The increase in 1935 was not due to the use of glucose solution but is explained by the fact that more patients were treated in that year. None of these reactions were at all dangerous and they were easily controlled by the usual methods.

CONCLUSIONS

It is apparent that in a great majority of cases intensive pollen therapy with high doses (30,000 to 60,000 pollen units) will markedly reduce scratch tests previously strongly positive, and in many cases (14.9 per cent) they will be extinguished. Clinical relief occurred in some cases without much change in skin sensitivity. It is apparent, however, that the majority of clinically good results parallels diminution in the scratch tests.

It was noted that the larger the initial skin reaction, the greater the diminution of the tests after treatment.

The cases showing smaller skin reactions were more refractory to reduction.

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DISCUSSION

DR. I. S. KAHN, San Antonio.—Dr. Levin was kind enough to send me a copy of his paper, and I feel that all of us who are honest with ourselves are not perfectly satisfied with the results we are securing in preseasonal pollen therapy. We have too many failures and too many cases that just barely get by. This work has been done a great many years, and I think on the whole we are not doing nearly so well as we ought to do. I do not feel competent to discuss the effects of these massive doses on the skin tests because I have not done enough of them.

When Dr. Brown reported before this organization two years ago his revolutionary method of treating with these extremely high preseasonal dosages, with far better protective results than most of us can secure, he was rather ridiculed; however Dr. Levin's similar results, far better than average with somewhat similar dosages, make one wonder whether more conservative men are not actually incorrect in adhering so strongly to such conservatism.

My own interest in this matter lies in the fact that it has seemed to me logical in the sixteen weeks' time I have usually allotted for this purpose to attempt to reach as high a preseasonal dosage as this time limit and local reactions would permit, stopping with 0.5 c.c. to 1.0 c.c. of a 1:50 extract for a final dose (0.1 c.c. to 0.2 c.c. of a 1:10 extract), raising very slowly, 0.1 c.c. at a time, at weekly intervals after reaching 0.3 c.c. of the 1:50 extract. In a few instances I have been willing and able to double this final dose, invariably with excellent results when I had done so. The highest dose of ragweed I have ever given was 0.24 c.c. of a 1:10 extract four years ago with a perfect result; however this patient in three successive years did just as well under a dose one-half as large.

I have had no constitutional reactions for years. My dread of such a possibility and its prevention by care in not raising doses in the face of local reactions of any size have prevented in this length of time, except in rare instances, my passing my usual maximum dose mentioned, however desirous I might have been. At present I am starting new patients where possible to do so, as does Dr. Brown, from eight to nine months ahead of the season. This gives plenty of time to overcome by several dosage repetitions any local reactions of consequence that will ensue. How practical this will be, I do not know.

Another revolutionary point in Dr. Levin's method is his injections in the same area in spite of local tissue reaction exhaustion possibilities. Personally, I have always varied injection sites, considering the local reactions my best guide to tolerance for the time being. I have no constitutional reactions. He has from five to eight a year, easily controlled and doing no harm. On the whole, his results are somewhat better than mine; however the almost perfect results I have had in the few patients in whom in this time period of sixteen weeks I was able and willing to reach 1 c.c. doses of a 1:50 extract with no reaction or only minimal reaction, lead me to believe that this large dosage method, when possible of attainment, offers a distinct improvement in our methods, and I personally am acting accordingly. I do not like constitutional reactions, hence my long preseasonal start.

DR. ALAN G. CAZORT, Little Rock.—I have been retesting such patients for a number of years. I have tested many of them several times through the year, and some are on perennial treatment. My

object is to try to reach 0.35 c.c. of a 1:20 dilution. If I can get the patient up (and I think this is the experience of a good many men) to within anywhere near that size dose, I find a marked diminution in the skin reaction. I cannot get many of them that high. I have treated patients as long as two years and I cannot get that high because I am a little afraid, like Dr. Kahn, of those reactions. But if you will get the patient up and hold him there, I think there is no doubt that you will find the skin reaction greatly reduced, and the skin reaction is a pretty good measure of the patient's sensitivity to the pollen. I insist that we must remove the foods and other offending allergens if present, and they usually are present, to get results.

DR. ROBERT W. LAMSON, Los Angeles.—Certain of the earlier investigators, notably Drs. Cooke and Coca, held the belief that skin reactions were not decreased after pollen therapy. They emphasized that this was true whether or not clinical improvement resulted. I have one of Dr. Cooke's original patients to whom he has given 11 or 12 consecutive seasons of pollen treatment with complete relief of hay fever. I have treated her for an additional two years, and at each retest she gives as intense pollen reactions as any untreated patient I have observed. A few patients of this type are known to each allergist, but I believe they are the exception rather than the rule. It is not, in my experience, necessary to give enormous pollen doses to effect a reduction in the intensity of skin reactions. This usually occurs after one to several seasons of adequate treatment. Clinical relief may, of course, be obtained without evident change in skin sensitivity.

Tests made immediately after discontinuance of treatment may show a decrease or be entirely negative and several weeks later become positive. Intracutaneous tests only were used in the study reported from Dr. Piness' Clinic. These were done several months after a course of treatment, and hence the decrease in skin response represents a real trend rather than a transient hyposensitivity.

DR. R. H. FINNEY, Pueblo, Colo.—Dr. Gauss and some of the rest of us in the Rocky Mountain region have to face a different problem than many of you in the East and South, where you have ragweed as the principal factor and sometimes the only one. We in the West do not have that as the principal causative agent.

Dr. Kahn brings up the question as to many pollens causing hay fever. We are treating not only with one, but sometimes with a half dozen antigens, and in that case the problem is made more complicated in our dosage. We get a multiplicity of antigens, and we have to be very careful and cannot get up into the higher dosage as you can with only one antigen. You have an easier problem in the East.

DR. NARCISSE F. THIBERGE, New Orleans.—The digest of the paper read by the essayist is that the test is an expression of a person's immunity. I should like to ask the essayist the question: How is it that when patients present themselves for testing during an acute attack, no adrenalin having been given, their reaction is negative, and yet, on a subsequent visit, after they have overcome the acute spell, their reaction then is *not* negative? Were they immune at the time they were suffering?

We have observed such a reaction in over 5,000 patients and tested backward and forward after treatment and during treatment. The results

were rather confusing, and the impression was that the response to the test was in no way an expression of immunity. I should like to raise that point and ask the essayist whether he thinks that a negative reaction is an expression of sensitization, desensitization, or immunity.

DR. ABRAHAM H. FINEMAN, New York.—Has the essayist had any children in his series of cases?

In our experience we have had very good results in children with hay fever and pollen asthma and use only moderate or less than moderate dosage of pollens. At no time do we use such massive doses.

My second question is: What percentage of constitutional reactions did he obtain in this group as compared with other patients on much smaller dosage?

DR. DUKE, Kansas City, Mo.—In discussing pollen dosage in therapy very few physicians take into consideration the varying effect pollen extract has, depending upon the rate at which it is absorbed: in other words, the rate at which it gets into the blood stream and can circulate and affect the tissues generally.

When a physician gives a dose of pollen extract, the dose given subcutaneously is one thing, the rate at which it reaches the blood stream is another thing, and varies not only with the place at which the extract lodges (in a venule, lymph space, or extravascular tissues), but also with the reaction produced at the site of inoculation. Cohen has compared a local pollen reaction with the Arthus' phenomenon and as was shown in the case of Arthus' phenomenon has demonstrated that a local pollen reaction actually retards the rate of absorption of the extract. In other words, the local reaction itself holds the extract local. It is frequently noted that, when patients give enormous local reactions to an injection of pollen extract, the therapeutic effect of the extract is less likely to be the usual. I believe frankly this is due to the fact that the pollen which is injected does not get into the blood stream fast enough to give the expected effect.

I think some of the variation in results obtained in pollen therapy is due partly to the fact that in a given therapeutic method the actual dosage which persons receive in their blood stream varies and that the top dose which we find necessary to protect the great majority of individuals is not in actuality a top dose for certain individuals who give large local reactions to the pollen. In pollen therapy in my own work I believe that I reduced the effect of therapy to a more constant standard by mixing adrenalin and ephedrine with the pollen extract and by giving it always distal to a tourniquet which holds the extract local until the vasal constrictants have had their physiologic effect. This method has been described in a previous communication and need not be repeated here. The technic which I use, however, has more constantly given a reduction in positiveness of cutaneous tests than any method which I have used.

DR. B. G. EFRON, New Orleans.—One of the biggest troubles in reading the literature on this subject is that all of us seem to be talking in a foreign language to each other. Up to the present time, we have absolutely no standards for our extracts. For several years a 3 per cent pollen extract has been considered by many as the strongest possible extract that could be made. Stronger than 3 per cent extracts have been discouraged.

We have made extracts in 1, 3, 5, and 10 per cent strength (weight by volume), and by means of our (Dorfman and Efron) method of assay with skin tests using the cutaneous technic we can definitely say that extracts containing the greater amounts of pollen contain greater amounts of active substances. Clock's work is open to serious criticism, because if you look on his article, "Comparative Value of Methods of Preparing Pollen Antigen," you will find that one of his extracts was made with what he describes as a 66.6 per cent glycerol solution. What made up the other 33.3 per cent of this extractive?

DR. PESHKIN.—Saturated salt.

DR. EFRON.—Saturated salt solution and glycerine was one extractive. I am referring to his extractive which he labels "C." Here he merely states that the pollen mixture was extracted in 66.6 per cent glycerol. No mention is made of what constituted the other 33.3 per cent. The solution, constituting this third, is of the utmost importance, since Clock stresses the fact that the salt and glycerol extraction was the most potent, whereas the glycerol extract (C) was only 40 per cent as strong as the extract prepared in glycerol and salt. Glycerine is not an extractive; glycerine is a preservative.

I do not understand what anybody means, and I venture to say most of you do not understand what a pollen unit is. Until such time as the active allergic principle is isolated from pollen, we have no business speaking of pollen units. To date we have no accepted standard. Neither the total nitrogen nor the protein nitrogen can be accepted as the standard of activity, since the nitrogen represents both active and inactive fractions in the extract. We keep on talking about protein and pollen units when we know the methods we use for determining them are erroneous.

With reference to constitutional reactions in using doses as high as 1 c.c. of 5 per cent and 10 per cent extracts, we find that if we are going to get constitutional reactions, they are much more frequent at the lower dilution than they are in the concentrated extract.

DR. WARREN T. VAUGHAN, Richmond.—We are making statements in our discussions of papers, which appear in the transactions, and are quoted thereafter, finally getting into the general literature. I think Dr. Efron's cautionary remarks are very good, but we must be careful in making positive statements during discussions to be sure that they are authenticated.

Now, if Dr. Efron, who has very definitely stated that the glycerine changes the concentration of the extract, has tried to make extracts in pure glycerine, I should like to know more about it, especially concerning nitrogen concentration and skin test reactions.

DR. ALBERT H. ROWE, Oakland, Calif.—I believe that this paper is extremely important, that it is going to clarify a certain indecision that is now in the literature. I shall be interested in knowing what percentage of negative reactions Dr. Levin gets after he has carried these patients on with perennial treatment for two or three years. When he has continued the perennial treatment of these patients, the percentage eventually showing negative scratch reactions will increase.

I also find better results in pollen therapy when a marked reduction or practical disappearance of the scratch test occurs. Thus I favor

perennial therapy in most cases. When patients can pass through a pollen season without symptoms and a marked reduction in skin sensitivity has occurred, more hope of an eventual symptomatic cure without therapy arises.

In California it is often necessary to treat with antigens containing grass, artemesia, amaranth, atriplex, and occasionally franseria pollens at the same time. With continued perennial therapy, marked reduction and at times disappearance of scratch reactions occur, with total doses of from 2,000 to 10,000 units of the important pollens. The dose of all the pollens injected often rises to 40,000 to 100,000 units, however, which suggests that such total dosage of all pollens is as effective in reducing skin reactions as is the high dosage of a single pollen. In fact, a nonspecific effect is probable, explaining why reactions to tree pollens or even to animal emanations are greatly lessened or eradicated in a few individuals who are treated only with large doses of grass or weed pollens. This, however, does not minimize the great importance of therapy with pollen antigens containing specific tree, grass, or weed pollens of those important species to which the patient is actually exposed during his season of symptomatology.

Dr. Milton B. Cohen, Cleveland.—The difficulty in discussing this paper results from an absence of a very essential control.

Before we can determine what happens to skin tests as a result of treatment we must have a study of the same patients' skin reactions at intervals during a year before treatment. When we have this background information, we may be able to decide.

Dr. Ben Z. Rappaport, Chicago.—There are too many variables involved to come to definite conclusions by comparing the size of skin tests at various times. First, with Hill's instrument the depth of the cut varies with the pressure applied. In addition, hay fever patients vary when the reaction is compared preseasonally, during the season, and after the season, whether treated or untreated. In women in most cases there is a definite difference related to the menstrual cycle.

Dr. M. Murray Peshkin, New York.—Last year I read a paper before the society on "A Critique of the Perennial Treatment of Pollen Allergy." In that paper I called attention to the protocol which showed with all methods of testing, what occurs to the pollen test reactions in patients treated by the preseasonal and perennial methods. As a result of pollen treatment, the scratch reactions to concentrated pollen extracts in many patients subsequently became negative, but in a certain number of these patients the intradermal tests remained positive. In many instances, however, the intradermal reactions to a 1:50 dilution of pollen also became negative. A few patients ultimately reacted negatively even with the dry pollen ophthalmic test. In the cutaneous refractory cases the average top treatment dose reached was not more than 1.25 c.c. of a 1:50 dilution of pollen. Despite the eradication of cutaneous (scratch and intradermal technics) and even ophthalmic (by dry pollen technic) reactions as a result of, or incidental to, pollen treatment, there were a certain number of patients who still showed some degree of pollen intolerance. In other words, in the patients in whom the eradication of pollen test reactions was accomplished,

complete immunity from pollen symptoms was not always obtained. Moreover, all these patients also failed to show the presence of blood reagins by the passive transfer test.

In view of these findings it appears that the determination of the degree of reduction of pollen test reactions by the scratch technic holds little significance, since the complete abolition of scratch test reactions does not imply that the intradermal test will be negative. As a matter of fact, the abolition of test reactions by any technic of testing does not imply that clinical immunity has been conferred upon the patient.

DR. LEVIN.—I want to say, going through the paper as fast as I did, that I did not cover some of the points that I have been asked about. If I had, I think this excellent discussion might have been cut down to some extent.

First of all, I think there is a difference in where you are treating hay fever. Those on the eastern coast do not have the pollen concentration we do, and do not have to go so high. I want to emphasize we did not go as high as we did to try to obliterate the skin tests at all. That was incidental. Previous years' experience told us we were not getting the results with lower doses. We made the scratch tests as a matter of curiosity, and finally made it routine, not only at the beginning and end of the season, but occasionally during the season. I did not report these, but they kept going down right along.

As far as the intradermal tests are concerned, there was no attempt to show that the patient was completely desensitized and was free of all reagins. It was simply a report of what happens to the scratch test done in a uniform way before and after treatment, using such top doses. There was no other intent behind the paper whatever, nor was there any intent behind the paper to convert you to using high doses, because your situation is different, perhaps, than mine. I do not know what you do in Kansas City or Buffalo, but I know you do not need to do this in New York City or in Atlantic City. Some of my patients who used to go to Atlantic City in the middle of a hay fever season had no hay fever there because their hay fever came only with the tremendous amount of pollen we have around Detroit. Perhaps the reason for the reduction in skin tests not being seen by others is because their patients have not needed such "huge" amounts of pollen. I want to put quotation marks around "huge," because to me they are not huge amounts.

As to the extracts, there was not the slightest difference in results between the 3 per cent coca-glycerine and the 5 per cent glucose solutions; nor any difference at all in the protein nitrogen, or total nitrogen content, and these were checked repeatedly. There were not a great number of general reactions seen. In 1933 we had five; in 1934 we had six; and in 1935 we had 8. The latter apparent increase was not because we used the glucose solution in 1935 but because we had more patients to treat. We treated 50 per cent more in 1935. These reactions were not dangerous. I am excluding the minor reactions that occurred after a patient got home, such as a few sneezes. I am talking about reactions which usually occurred within one hour and had to have adrenalin. None of the reactions were dangerous in any way.

We did not treat for ragweed alone. We used in some cases cocklebur and wormwood sage. Also I did not mention the spring cases. We found the same thing occurring with those pollens. I did not make

routine skin tests for other factors unless the patient had perennial symptoms. After the first year, after reaching as high a dose as this and not getting a good result, I made routine skin tests for the subsequent year.

I think one reason some men do not get as high as this without more reactions is that they do not give the injections deeply in the same site in the same arm every time. After the first four or five injections there is practically no local reaction at all. It is a desensitized site, I think.

As far as the statement by Dr. Duke that we may not be giving that dose all the time, it is hard for me to visualize that anything can happen to the pollen extract after injection, except absorption. It must get into the circulation, even though slowly. It finally gets in, even though absorption is slowed down by local desensitization. I have always used adrenalin with each injection with the high doses, but right from the first dose, 0.02 to 0.05 c.c., depending on the patient's sensitivity to adrenalin. When very sensitive to adrenalin, we have to dilute it 1:10.

There is the other point about the skin tests. A positive test does not necessarily mean that the patient is clinically sensitive. Also, we all know that a clinically sensitive patient may be negative to the intradermal test. It may show up only in the eye. I excluded these patients from this report. In the individual patient the changing skin test is apparently a criterion of changing clinical sensitivity. It is an individual matter. In other words, if the patient starts with a three-plus reaction instead of a four-plus, he may have worse ragweed hay fever than the four-plus case, and as it goes down, it is an indication of what is happening to clinical sensitivity.

We know we get patients clinically sensitive to an exquisite degree who are negative to any kind of skin reaction. I also pointed out that the larger the initial skin tests, the greater number of them were reduced. In other words, the ones showing smaller initial skin reactions were more refractory to reduction, and that brings up the point of how we treat the patients who show no skin reactions. We start much higher, and use even higher final dosages, running up to 3 c.c. of 3 per cent extract.

How many children do I treat? First of all, I am a pediatrician and then an allergist. About 50 per cent of this group were children, and the average top dosage in children was 1 c.c. of a 3 per cent solution. I shall not use the words "pollen unit," since some object; but you know what I mean, supposed to contain 30,000 units per c.c. of 3 per cent solution.

INFLUENCE OF WEATHER ON BLOOD DENSITY, PLASMA VOLUME, AND WHOLE BLOOD CHLORIDE*

J. H. Black, M.D., Dallas, and A. H. Braden, M.D., Houston, Texas

IT IS a matter of common knowledge that the weather has a profound influence upon the allergic mechanism. Many persons suffering with asthma can foretell with considerable accuracy an impending weather change before it becomes recognizable to the nonallergic person. Most of them will volunteer the statement that their asthma is worse when weather changes occur, and particularly do they say that damp weather aggravates their condition. There are many allergic persons, also, whose symptoms may be prominent during the fall, winter, and early spring but who remain quite free of symptoms during the hot dry weather of summer as we see it in the southwest. Many of these, we believe, present symptoms or are free of them largely dependent upon weather conditions and not because of seasonal exposure to allergens or bacterial invasion. In some instances it has been possible to show that a food-sensitive person may be able to eat the offending food in moderate amount during hot, dry weather but must omit it from the diet in variable weather of other seasons.

With the advent of air conditioning there have been investigations into the effect on pollen-sensitive persons of control of pollen, temperature, and humidity. Rappaport, Nelson and Walker[1] made such a study and found some attacks of asthma occurring during storms although the pollen, temperature, and humidity were adequately controlled. They suggest that the barometric pressure and ionization of air might possibly play an etiologic rôle.

Although it may be admitted that weather conditions greatly influence allergic reactions, no study seems to have been made to determine how weather conditions affect the allergic mechanism. This doubtless is due to our ignorance of the mechanism of the allergic reaction, but it is possible that information regarding the influence of weather changes might throw some light on the allergic reactions themselves.

On the assumption that local edema is an underlying condition in the allergic reaction, it would seem logical to assume that any condition which would cause a flow of fluid from the blood to the tissues would predispose to an allergic attack or make one possible from a specific allergen which, of itself, might be insufficient to provoke an attack. On

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this basis we have studied the red cell volume, blood density and chloride content of whole blood under varying conditions of humidity and barometric pressure.

Elsewhere[2] we have reported the finding of an increase in blood concentration in artificially induced hay fever, showing that approximately 3.5 per cent of the fluid portion of the blood left the vessels immediately on the onset of nasal symptoms causing an increase in the tissue fluid (Fig. 1). This is similar to the concentration which occurs in the anaphylactic guinea pig.[3]

One of us (J.H.B.), sensitive to ragweed, was used as the subject for cell volume studies which were made outside the ragweed season and in the absence of allergic symptoms. Blood was secured from a vein be-

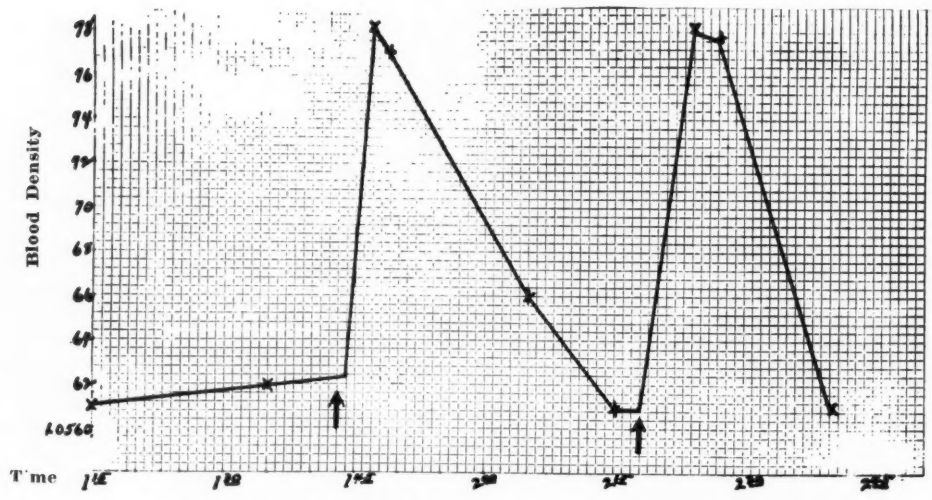

Fig. 1.—Changes in blood density in hay fever (artificially induced).

tween four and five hours after a light midday meal. All conditions regarding the intake of food and fluid, work, and room temperature were kept within narrow limits. The variable factors were the barometric pressure and the humidity. Blood was drawn without a tourniquet to avoid changes in concentration due to venous stasis and 1 c.c. of a 1.6 per cent sodium oxalate solution (which is practically isotonic) added to 5 c.c. of blood was used as an anticoagulant.

Under the above conditions hematocrit determinations were made. It was recognized that red cell volume is probably an unsatisfactory index to total blood volume, but it was believed that changes in the cell volume would serve as a reliable criterion of proportionate changes in the plasma. Fig. 2 shows a series of cell volume determinations with the barometric pressure and relative humidity readings taken within an hour of the time the blood was drawn for examination. It will be seen

that, while there is wide variation in the pressure and humidity readings, the hematocrit readings were practically constant.

Recognizing that the cell volume determination is probably too crude a method to detect changes which might occur, we did a series of blood density determinations using the method of Barbour and Hamilton.[4] This consists of the timing of the fall of a 10 c. mm. drop of blood through 30 cm. of a mixture of xylene and bromobenzene. The falling time of a similar size drop of potassium sulphate of known specific gravity is determined and the specific gravity of the blood calculated.

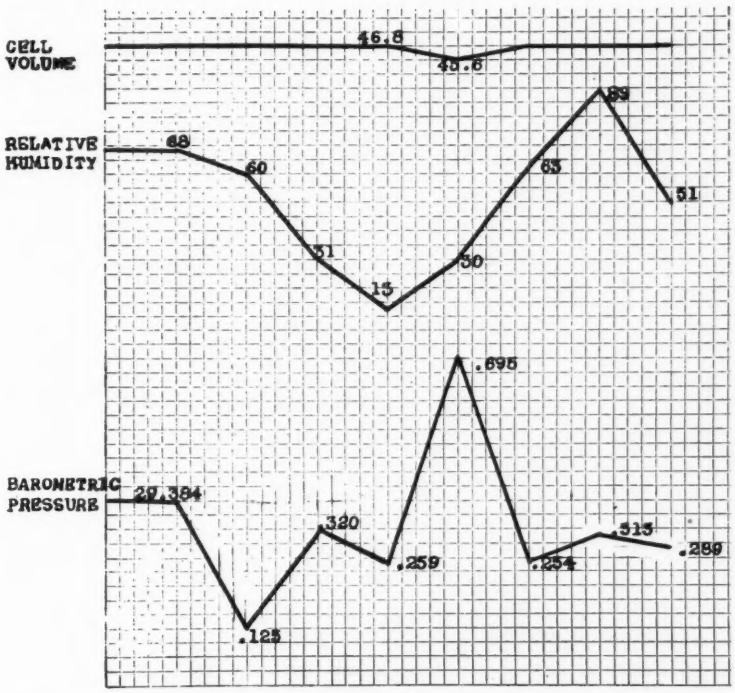

Fig. 2.—Constant cell volume uninfluenced by humidity or barometric pressure.

It is a method which permits the use of a small drop of blood, can be quickly and frequently repeated, and detects very small changes in density.

Fig. 3 illustrates a series of such determinations made on one of us (J.H.B.) together with the barometric pressure, the relative humidity, vapor pressure, and temperature readings obtained at the same time. The conditions under which the blood was drawn were similar to those in the cell volume determinations.

It may be seen that definite changes in blood density occurred from day to day extending over a range from 1.0566 to 1.0598, which is equal to a change in water content of 6.4 per cent. The barometric pres-

sure curve is strikingly similar to the blood density curve, an increase in density occurring at the time of increased pressure. The relative humidity and the vapor pressure readings were just the reverse, high density being associated with low humidity. The temperature showed only small variations (a range of 7° C.) and, while a rise in temperature is associated with a decreased density, is not so definite as are the other factors.

Blood chloride determinations in allergic persons have been reported by several investigators. Most of these made no mention of whether determinations were made during attacks or in the free intervals, and none seemed to take into consideration possible variations in blood

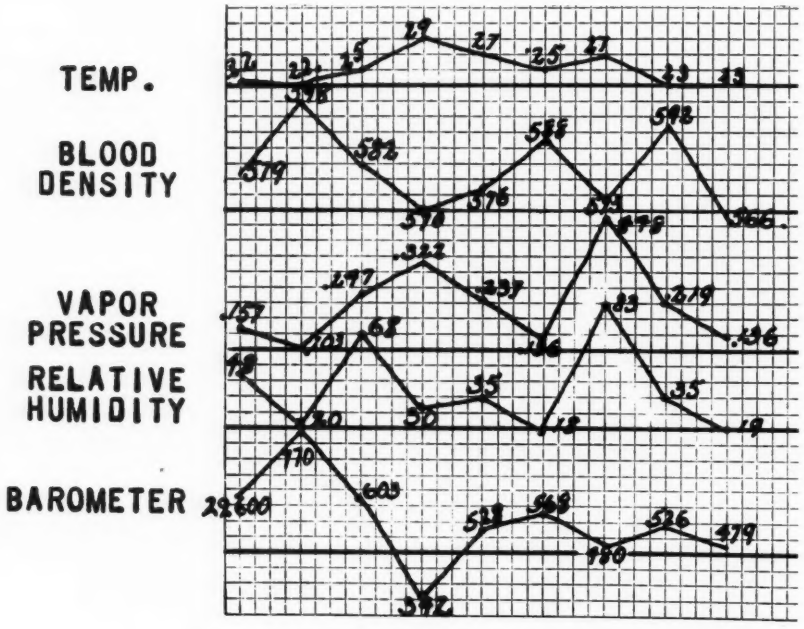

Fig. 3.—Blood density and weather conditions.

volume. Since it is apparent to any one who has observed asthmatic attacks that there must be considerable water loss from muscular activity and perspiration, changes in blood concentration would be expected. Since it is known that the plasma contains much more chlorides than do the red cells, a loss of fluid should cause a definite reduction in the whole blood chlorides. Barber and Oriel[5] state that the whole blood chlorides are diminished in acute and chronic allergy, that this finding is most constant in the asthma-prurigo group and that it varies with the exacerbation or remission of symptoms. But apparently no blood volume studies were made to determine whether the findings were part of the allergic reaction or solely a result of loss of blood fluid.

We have done whole blood chloride determinations on 90 allergic patients. Twenty-four of them were having mild attacks of asthma at the time of the examination; the others were free of symptoms. Of the 24 showing symptoms 10 showed varying degrees of blood concentration as determined by cell volume. Of these, 4 showed low chlorides and 2 were above the normal limits. Eight showed no evidence of concentration but 6 of these had low chloride content. Six showed increase in plasma content, and of these, 4 had high chloride readings while the other 2 were low.

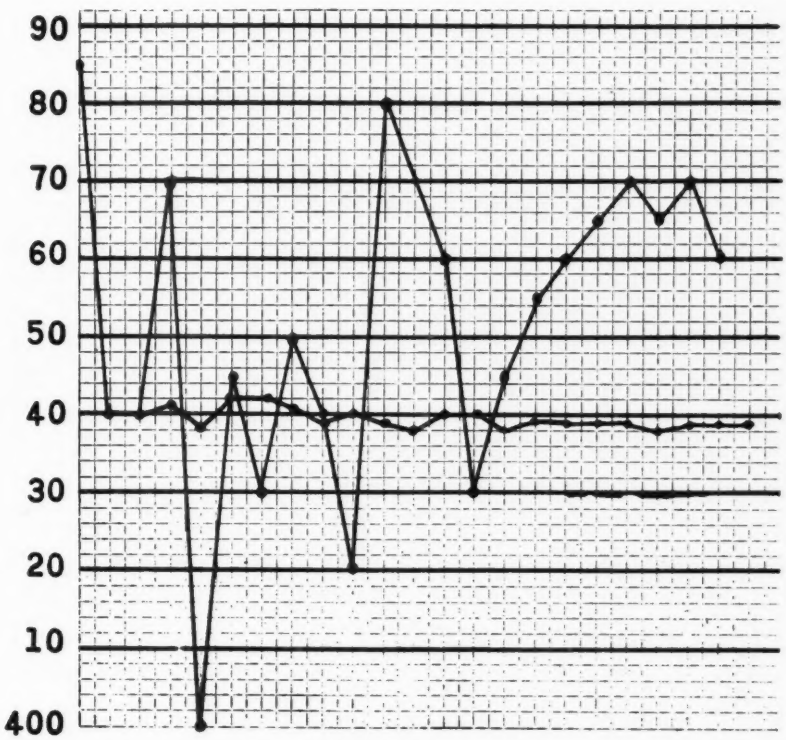

Fig. 4.—Blood chlorides and red cell volume.

The chloride content of the blood of 66 persons free of allergic symptoms at the time of examination showed wide variations, ranging from 310 mg. to 544 mg. The average of these readings was 416 mg. In contrast with these was an average reading of 426 mg. in the patients with mild asthmatic attacks. Of the 66 persons tested in their free periods 10 had some degree of blood concentration with low chloride readings, while 30 had low chlorides with no evidence of concentration. The others had normal readings with no evidence of blood concentration.

Fig. 4 shows a series of chloride and cell volume determinations made on one of us (J.H.B.) to determine daily fluctuations. These were made

under the conditions recited above in the discussion of cell volume determinations. It may be seen that while the cell volume remained relatively constant the chloride content varied from 485 mg. to 400 mg.

CONCLUSIONS

There are daily variations in blood concentration which may be determined by the method of Barbour and Hamilton. These occur in the absence of allergic symptoms and may be related to humidity and barometric pressure. Cell volume determinations do not detect these variations.

Blood chloride determinations should be correlated with blood volume at least in attempting to show differences in and between attacks of asthma. The variation of whole blood chloride content of the blood is considerable under normal conditions, and significance should be attached only to wide differences.

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DISCUSSION

DR. CHARLES N. HENSEL, St. Paul.—These figures are interesting, but Dr. Braden has not told us whether he had controls as far as the blood chloride and blood volume are concerned. Were these people on a basic sodium chloride intake and fluid intake?

DR. OSCAR SWINEFORD, JR., University, Va.—I am terribly sorry that Dr. Braden did not permit himself the luxury of a hypothesis. I have permitted myself that luxury and I may as well express it here. It is this: barometric pressure frequently varies 10 to 20 mm. of mercury or 140 to 280 mm. of water. With this variation in external pressure there must be some adjustment of the intravascular osmotic pressure. Without this adjustment one would expect extravasation into the tissues when the barometer falls and dehydration of the tissues when it rises. Metabolites would presumably collect in the tissues during the period of extravasation. The mechanism with which the normal person adjusts himself to these changes is not known. Nor is the reason for the failure of the abnormal person to adjust himself known.

Sodium chloride is only one constituent of the blood stream responsible for its osmotic tension. In the normal individual the chlorides fluctuate widely under a number of conditions difficult to control. I believe that much more conclusive information could be obtained by studying at short intervals the osmotic tension of the whole blood with some of the

dialyzing apparatuses recently described. I hope the authors have the facilities and the desire to pursue this further, as their problem is most important.

DR. ROBERT W. LAMSON, Los Angeles.—For a number of years I have been interested in climatic effects upon allergic conditions. At certain seasons of the year, notably September to October, and again in the spring, there seems to be an increase in respiratory allergic symptoms. This occurs in the non-sensitive as well as in the sensitive individual and with or without contact with the specific excitants. Changes in the clinical or physical conditions of the blood may cause these symptoms, or be the result of them.

At the same periods of the year, especially the fall, the incidence of so-called colds in the normal population shows a very sudden rise. I refer to the type of complaints which do not require medical attention, and so do not ordinarily get into vital statistics. The U. S. Public Health Service has published such a study (Public Health Reports, Vol. 47: 1815, September 2, 1932), and they show very little variation of incidence in the six sections of the country represented. I believe that some climatic factor is responsible for the sudden onset of respiratory symptoms in the normal, and at the same time in the allergic, group. The latter group does not commonly present symptoms of a true infection. I wish to compliment Dr. Black and Dr. Braden for emphasizing that one need not assume a new bacterial infection to account for a sudden aggravation of symptoms.

I should like to make this propheey, that no matter where or how you may be treating asthma and hay fever the phenomena mentioned will be repeated again this fall in the normal as well as in the allergic population.

DR. BLACK.—Contrary to Dr. Swineford's statements, we did have a hypothesis, but we had it first. The hypothesis on which we started this work was that there probably was a change in blood density due to weather conditions, and we were hoping to find that with an increase in humidity and a drop in barometric pressure we would find an increased density of the blood which would mean the fluid had gone out into the tissues. On the assumption that had taken place with an increased edema, it would take much less excitant to bring about an allergic attack than at other times, and we felt the weather might influence the asthmatic person in the particular manner that when at one time there is more fluid in the tissues, an individual can be more easily drawn into an attack than otherwise; but the results were directly contrary to that.

The third slide showed the density and relative humidity and the barometric pressure; that when the humidity went down and the barometric pressure went up, the density also went up. When the humidity went up higher, we expected that the individual was more likely to have an attack, that the blood density would go up, showing more blood going into the tissue; but the exact opposite occurred, so we had to abandon our hypothesis.

In regard to Dr. Hensel's statements that these patients should have been on a basic diet, I think possibly we did not make ourselves clear as to why we were doing this. We were not attempting to show the blood chloride content of individuals under optimum circumstances, but that the chloride determinations under ordinary circumstances were not very dependable. The last slide which was shown was a series of 21 consecu-

tive chloride determinations, done on myself on 21 consecutive days. These were done without a tourniquet. A tourniquet on the arm for five minutes will make as much as 30 per cent difference in plasma volume. If that is true, the tourniquet has a tremendous influence; and these were made without the tourniquet, simply putting the needle into the vein. They were done outside the pollen season when we were having no allergic reaction at all, four hours after a light midday meal; and while that was not always exactly the same, neither is the preceding meal in the ordinary individual.

When doing this blood chemistry—no food for four hours and no fluid for two hours—under those circumstances you find the chloride running from 400 mg. to 485 mg.

Recently there was an article in the *Journal of Laboratory and Clinical Medicine*, on blood changes following hyperthermia, in which it said there were changes in blood chloride in a range of 2 per cent, and here we are finding in a normal individual under controlled circumstances a variation of 85 mg. The only reason for presenting this is the fact that if we are going to do blood chemistry determinations on these individuals, we ought to recognize first that blood volume does play a part and individuals suffering a large water loss in asthmatic attack should have that taken into consideration; and, second, that the variations are so wide that one ought to draw conclusions only on wide variations.

DIAGNOSIS AND TREATMENT OF SENSITIZATION TO MOSQUITOES*

ROBERT L. BENSON, M.D.
PORTLAND, ORE.

THIS report concerns itself with the occasional occurrence of a definitely specific sensitization to products of the mosquito. The avenue of entry is by the insect's sting, but the results have little in common with ordinary effects attributed to venom, and are, in the sensitized individual, out of all proportion to the amount of secretion injected. Before entering into a discussion of this special type of hypersensitiveness I shall first proceed to an account of four cases which I have diagnosed and treated, three of them with a successful outcome.

CASE 1.—This patient, Mrs. F. A. K., past fifty years of age, was diagnosed as allergic to insects by Dr. H. A. Koefod, of Santa Barbara, and referred to me in May, 1932. I found her sensitive to flaxseed and bovine epidermal extract, as well as to certain insects. She stated that as early as 1915 the bite of a black fly caused moderate local swelling and pain. Later in the same summer similar bites resulted in greater pain and much larger swelling, and persisted several days.

Mosquitoes never caused her any unusual discomfort until August, 1924. The first manifestation then was an inflammatory swelling at the site of the sting, without much pain, but with the formation of vesicles in the course of a few hours. In August, 1925, she received about thirty bites on a single occasion, and experienced in the course of hours intense swelling of the feet and legs, with severe pain and with increase of temperature. The appearance, she stated, was suggestive of erysipelas. From that time forth even single bites produced considerable swellings which started about six hours afterward and increased during the next thirty-six hours, with considerable local pain and the development of large central vesicles. On various occasions a single sting caused increase of temperature and cough, most intense forty-eight hours later. In the case of a sting below the elbow the swelling extended, within a day, below the wrist, and even involved the fingers. In all these instances the immediate wheal was insignificant, devoid of noteworthy pain or irritation, and the eventual reaction was of the delayed type already referred to. She reported that stings of different breeds of mosquitoes in various parts of the United States, Europe, and Africa, resulted similarly.

The foregoing details in the clinical history of Case 1 were, in general, similar to those of the other patients observed. It became evident at once that mosquitoes must be obtained in quantity. Fortunately the Bureau of Entomology and Plant Quarantine of the U. S. Department of Agriculture was at that time engaged, along with the City Nuisance Division, in a campaign to combat the local mosquito pest. Mr. H. H. Stage, Associate Entomologist of the Bureau, and his staff furnished me accurate advice, and also a continuous supply of living pupae of

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various species of mosquitoes. An adequate hatchery was installed, and in the course of a few weeks pure bred mosquitoes were grown, segregated, preserved, and classified according to the following criteria: (a) age—mature, young, and pupae; (b) sex—male and female separately; (c) species—*Aedes vexans, Aedes aldrichii, Culicella incidens.*

Preparations of the dried material were made according to several plans. The first and simplest was an extract of finely ground and etherized mosquitoes in Coca's solution. This, filtered through the Seitz filter, we designated "extract." The second, and equally important preparation, was obtained by extracting the finely ground and etherized mosquitoes in Coca's solution, and then precipitating with alcohol at

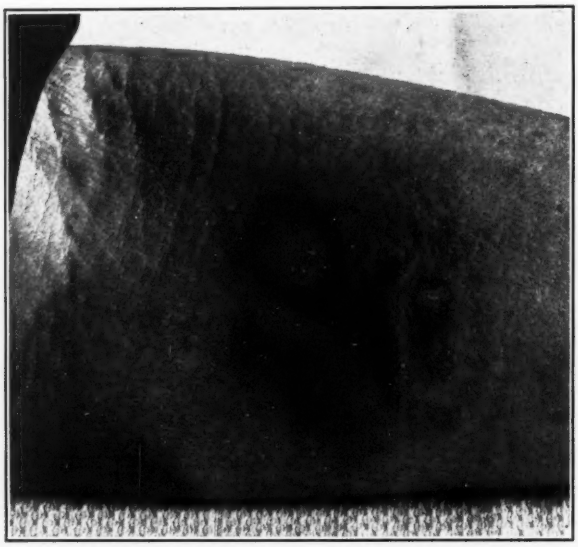

Fig. 1.—Case 1, nineteen-hour reaction to intracutaneous inoculation of 0.05 c.c. of 1:50 dilution of *Aedes vexans* concentrate.

0° C. The precipitate thus obtained, after repeated washings with cold alcohol and ether, and subsequent drying, was called "concentrate." A third fraction consisted of alcohol soluble material, dried and preserved.

TESTS ON MOSQUITO SENSITIVE PATIENT (CASE 1)

The so-called concentrate of *Aedes vexans* applied to the skin by the scratch method gave an immediate small wheal. At the end of twenty-four hours the site of inoculation was encompassed by an itching area of erythema 20.0 mm. in diameter, including in its center a wheal of 8.0 mm. containing several punctate vesicopapules.

Numerous intracutaneous tests were made at different times with dilutions of concentrate of *Aedes vexans* and *Culicella incidens* ranging from 1:5,000 to 1:50. A strength of 1:500 was required to give suitable

diagnostic reactions. The resulting early wheal was always small, and generally lacking in erythema, but was succeeded within twenty-four hours by a slightly raised erythematous areola 30.0 mm. in diameter, having in its center a flat nodule 10.0 mm. in diameter, and attended by moderate local heat and tenderness.

After having partially desensitized the patient by ascending doses of the higher dilutions I felt safe in making intracutaneous injections of 1:50 concentrate. The wheals following these were irregular in outline, with pseudopodia, and had usually a greater dimension of about 35.0

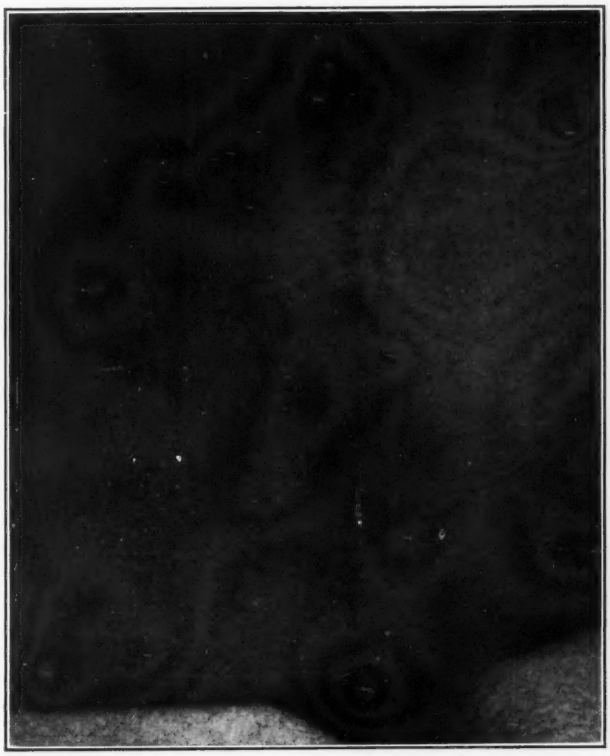

Fig. 2.—Case 1, twenty-one-hour reaction to intracutaneous test with 0.02 c.c. of 1:50 extract of newborn males of *Aedes vexans*.

mm. The reactions in twenty-four hours, which persisted for several days, were much more impressive, and were characterized by local heat, redness and discomfort. Fig. 1 portrays a typical infiltration of this type extending about one-half the length of the forearm. Non-sensitive controls failed to give reactions of significance.

In view of the fact that it is the female mosquito which inflicts the sting it might be predicted that extracts of the male of the same species would confer less reaction, or none at all. Experimentation has, however, not fulfilled this expectation. In repeated tests of the male and

female extracts performed in parallel on similar sites, the female product has never proved more potent than that of the male. In fact, the converse has usually been the rule (Figs. 2 and 3). It is evident that the infiltration following injection of products of the mosquito is independent of the sex of the insect, and therefore presumably not a component of the venom effect.

Neither is the age of the mosquito a significant factor, provided that we exclude the absolutely nonreactive larvae and pupae. Newly hatched mosquitoes, male and female, were segregated and their properties

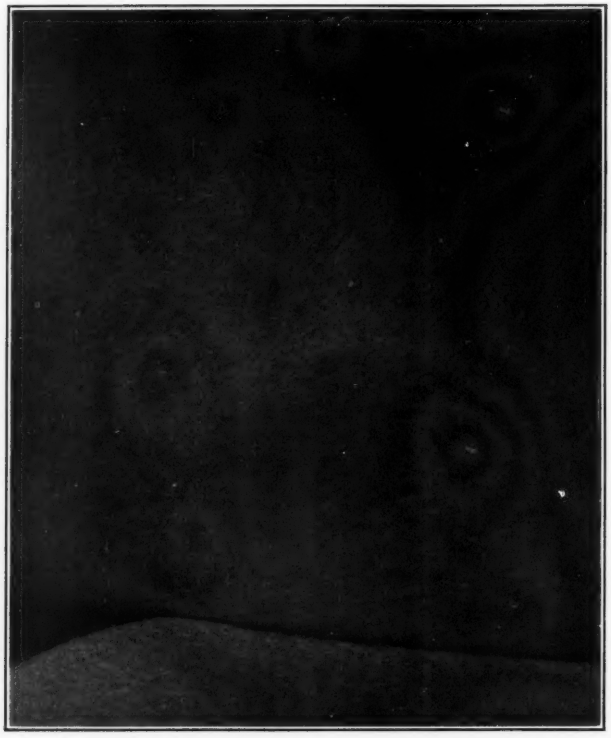

Fig. 3.—Case 1, twenty-one-hour reaction to intracutaneous test with 0.02 c.c. of 1:50 extract of newborn females of *Aedes vexans.*

studied. Their sensitizing qualities agreed entirely with those of the mature insects, and males were here again as reactive as females.

A total of about an ounce of dried mosquitoes, segregated according to species, was employed in the study, and included *Aedes vexans, Aedes aldrichii,* and *Culicella incidens.* No notable difference was found in their effects. It was even possible, by a single intracutaneous inoculation of extract of one species, to desensitize locally to subsequent injections of a larger amount of extract of another species (Fig. 4).

In one experiment the preliminary intracutaneous inoculation consisted of 0.05 c.c., 1:50 dilution of *Aedes vexans* concentrate. The immediate

reaction consisted of a definite wheal. The twenty-four-hour reaction was of considerable size. Two days later a second intracutaneous inoculation was made in the same site with 0.05 c.c. of the same 1:50 dilution of *Aedes vexans* concentrate. The resulting immediate wheal was fully as large as the original, but the reaction twenty-four hours later was negligible. Further tests proved that inoculation with one species and later reinoculation in the same site with material from another species likewise produced local desensitization as concerned the late reaction but not the early wheal. This abolition of the twenty-four-hour reaction of the

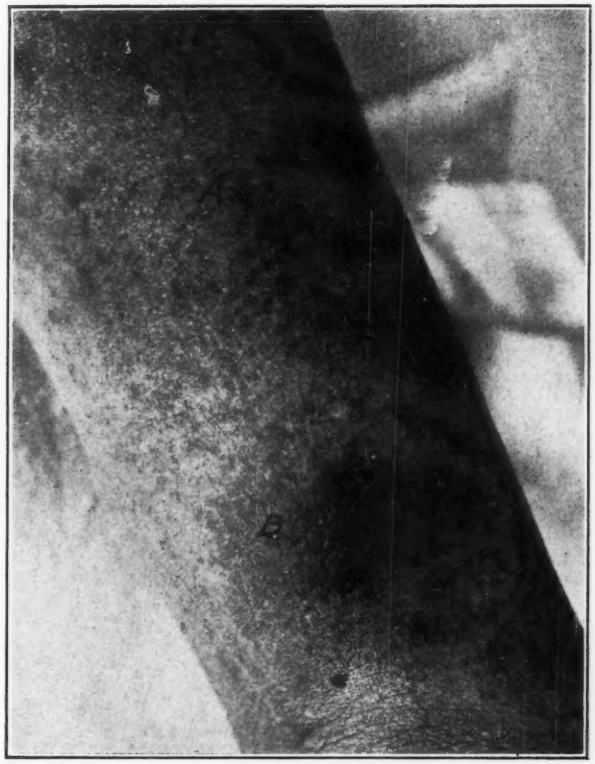

Fig. 4.—Case 1. *A*, Negligible twenty-four-hour reaction to intracutaneous test with 0.02 c.c. of 1:50 extract of *Culicella incidens* in previous inoculation site of *Aedes vexans* protein 1:50.

B, Twenty-four-hour reaction to similar inoculation with *Culicella incidens* extract in new site.

reinoculation, with failure to prevent the early wheal, requires explanation. It might suggest the possibility that the early and late reactions were due to distinct antigens.

A comparison of the separate effects of simple extracts and of concentrates disclosed a definite predominance of reactivity in favor of the latter. The method of concentration used made it appear likely that this strongly reacting precipitate contained a protein, or a protein-bound

antigen, which may have been concerned with the specific phenomena. Whatever its chemical nature was, it was certainly heat-resistant. Boiling for thirty minutes after the addition of a few drops of acetic acid failed to alter its reactivity (Fig. 5.).

Passive transfer was attempted repeatedly by the Prausnitz-Küstner method, but it gave varying results. A positive reaction of small size appeared in some instances, but on other occasions the method failed. I believe that transfer will be effected under ideal conditions.

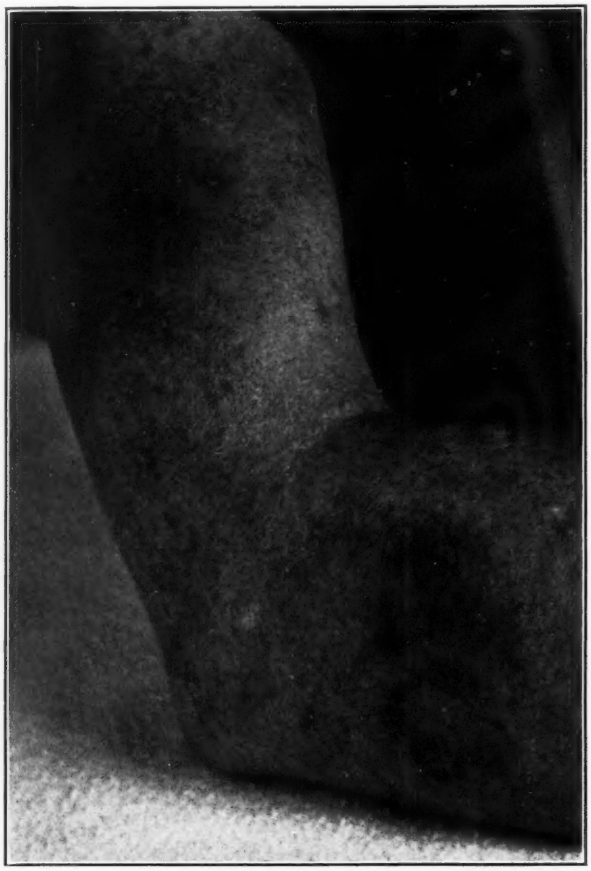

Fig. 5.—Case 1, upper areola is the twenty-four-hour reaction to the intracutaneous injection of 0.03 c.c. of *Aedes vexans* concentrate boiled thirty minutes with acetic acid. Lower areola, similar injection with unheated concentrate.

Before discussing the subject of the treatment of sensitization to the mosquito, I shall give briefly three other protocols.

CASE 2.—The patient, Mrs. V. R. H., aged thirty-three years, consulted me in June, 1932. She had been sensitive to the sting of mosquitoes for five years, the reactions being at their height on the second and third days. She became sensitive also to pollens in the spring of 1932. I tested her intracutaneously with 0.02 c.c. each of (a) *Aedes vexans* concentrate diluted 1:50, and unheated; (b) the same solution boiled thirty minutes with acetic acid and neutralized.

Each produced an early wheal under 10.0 mm. in diameter, followed within twenty-four hours by an area of erythema about 40.0 mm. in diameter. The patient received no further tests nor treatment, and yet was, in the subsequent four seasons, free from the complaint despite repeated stings. This unexpected outcome introduced the possibility of desensitization by a minimal number of inoculations.

CASE 3.—The patient, Mrs. H. J. B., aged forty-five years, had, when she consulted me in September, 1933, been troubled by mosquitoes to an increasing degree for several years. She came of an allergic family and was herself sensitive to certain foods, as well as to mosquitoes. During the following seven months she received intracutaneous tests with concentrate and extracts of *Aedes vexans* on 23 occasions. Very large erythematous reactions of the delayed type always occurred. Male and female products reacted about equally, and boiling for thirty minutes only partially destroyed the reactivity. The last and strongest inoculation, consisting of 0.02 c.c. of a 1:25 dilution of *Aedes vexans* concentrate, both male and female, produced a red, painful swelling within thirty hours, which extended one-half the length of the forearm and one-half the distance around it. During the subsequent two seasons the patient received no further tests or treatment, but despite many stings experienced no unusual discomfort from mosquitoes.

CASE 4.—The patient, Mrs. D. F., aged forty years, was sensitive to adhesive plaster, as well as mosquitoes, the latter over a period of more than twenty years. The sites of stings always swelled greatly, sometimes producing red streaks which extended up the arm or the leg. She was confined to the hospital at various times by such occurrences. The erythema was often several inches in diameter, and lasted from two days to a week. In 1917, while in military service in France, she received a sting on the left cheek, and within a few hours the resulting infiltration almost closed the left eye. The lip also became so swollen that for three days it was necessary to feed her with a tube.

I first saw this patient last summer, and during July and August gave her a total of six intracutaneous inoculations of 1:25 extracts and concentrates of *Aedes aldrichii* and *Aedes vexans*. All these gave moderate wheals followed within twenty-four hours by large, hot, painful swellings. From the time of the first inoculation she lost her sensitiveness to the sting of the mosquito. After the fifth inoculation I saw two sting sites, one on the wrist and one on the ankle, which had, in eighteen hours, caused no reaction of note.

DISCUSSION

It is obvious from the foregoing case records that all these patients exemplified a definite type of specific sensitization. The condition could not be construed as a mere intensification of the ordinary venom effect. The antigen, if not of a protein nature, was at least protein bound. Though injected along with the venom by the predatory female, it was also found to be present to even a greater extent in her docile and vegetarian mate. The newly hatched virgin female and the young unmated male already contained the sensitizing substance, but the pupae displayed no trace of it.

All the patients gave specific reactions to atopens—one each to pollens, foods, flaxseed, and adhesive plaster. Each displayed an early wheal of moderate size when tested with extracts of the mosquito. The outstand-

ing response in each instance, however, consisted of a large, hot, painful, somewhat raised erythema, starting within a few hours after the inoculation and gaining in intensity during the next twenty-four to forty-eight hours. This resembled the patient's reaction to the sting of the mosquito. Either the experimental or the mosquito-induced puncture may result in vesicles at the center of the erythema.

The sensitizing substance was found to be present in simple saline extracts. More potent, however, were the concentrates made by precipitation of aqueous or saline extracts by cold alcohol, and subsequent purification of the precipitate. Both types of preparation were used in testing and treatment. The antigen resisted thirty minutes' boiling in the presence of acetic acid.

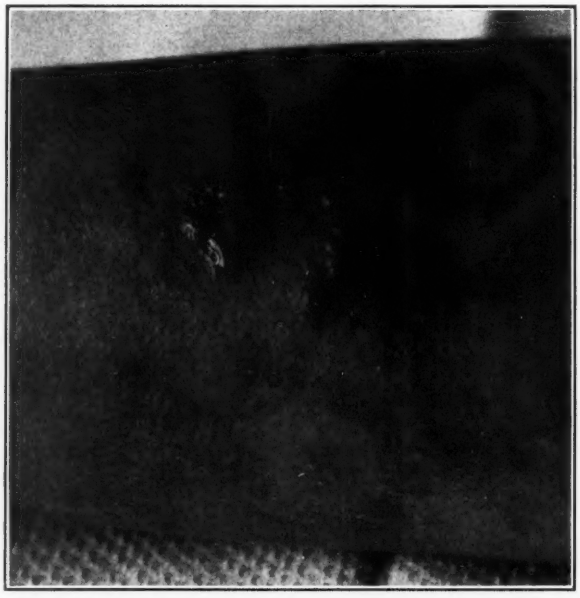

Fig. 6.—Case 1, forty-eight-hour reaction of seven mosquito bites in one area after patient had had considerable specific treatment. Note that this patient's inoculations have been only partially successful.

The last three patients became readily desensitized by very few, or at least a moderate number of, inoculations. Experiments disclosed that a single injection of dilute extract or concentrate desensitized the skin locally, not only to the same species, but to other species of the insect. The inference, from my experiments, is that repeated inoculations produced a systemic desensitization and afforded clinical relief to the patient. I have personally observed in two treated patients multiple stings which failed to cause discomfort.

The outcome of Case 1 requires special comment. This patient had numerous inoculations—possibly too many. She evinced a degree of local protection, and on one occasion received seven stings, intentionally

permitted, in one small exposed area. The result in reaction was typical, but much reduced in comparison with her previous experiences (Fig. 6). Instead of progressing with her desensitization, however, she again became more reactive to stings after leaving Portland. Dr. O. H. Stansfield, of Worcester, Mass., in an effort to solve her refractory state, tested her intracutaneously with alcohol soluble material of the mosquito which was sent by me. He reported a large reaction, persisting for days. Unfortunately, this patient's study was terminated by metastatic carcinoma of the lungs.

No other patient has reacted to the alcohol soluble material. Coincident with this fact specific treatment has been successful in all the other three cases. It is possible that injections which are carried on too extensively may confer a new sensitization to the alcohol extractives, including the venom. I recommend inoculations with extracts and concentrates of the mosquito, but always in moderation. The treatment is then hopeful.

RELATION TO OTHER INSECT STUDIES

In 1929, O. Hecht[1] described in detail the effects of the stings of various blood sucking insects on the skin of different individuals. He mentioned smaller or greater wheals which promptly vanished; those which were followed by a more persistent reddish swelling; and other stings, which, without other noteworthy reactions, resulted on the following day in a reddened, itching welt. Such differences occurred with closely related forms, as also with more distant genera. Various individuals also differed greatly in their degree of reactivity to a particular insect's sting. Thus he found that, contrary to the usual experience, his own skin failed to respond, visibly or subjectively, to the bite of the ordinary bedbug.

He recorded similar variations with certain species of mosquitoes, namely, *Stegomyia fasciata* and *Anopheles maculipennis*. In some persons the insignificant puncture reaction promptly faded, while in others the early papule was succeeded on the following day by larger red papules, which in some instances continued to increase in size and to itch for several days.

Of special interest is his citation of Martini[2] regarding local immunity. Working with "Waldmücken," a species of Aedes, Martini found the reactions to stings smaller in the newborn, and in adults who had previously been stung excessively. This citation gives a strong intimation of beginning tolerance in the newborn, later sensitization to the insects' stings, and possible desensitization by repeated exposure.

Hase's figures, as cited by Hecht, recite graphically the infinitesimal amount of poison injected in each sting. For the bedbug this aggregated only 0.0000167 c.mm. of saliva, and for the dog flea, 0.0000416 c.mm. Collection and measurement of the mosquito's saliva were not possible,

but the volume was surmised to be correspondingly minute. Hecht concluded that the toxic effects of the poisons of various blood sucking insects were exceedingly high, and that the amazingly small quantity alone prevented frequent and severe general reactions.

Hecht's experiments with different tissues of the mosquito were instructive. He made separate emulsions of the insects' salivary glands, the "Vorratsmagen" of the esophageal tract, the ovaries, and pieces of pectoral muscle. Each of these, injected intracutaneously into the human skin, produced effects entirely comparable with those of the insect's sting. These results were essentially corroborated by independent studies of Pawlowsky and Stein,[3] 1928. Hecht concluded that the poison of the salivary gland was in greater or less degree present in other tissues of the insect.

Bode,[4] 1933, reported what he considered a rare type of reaction to *Culex pipiens* in which spherical vesicles appeared on the skin, and could be transplanted with the fluid to other cutaneous areas. Hecht,[5] 1933, cited three additional similar reports, but considered the relationship of all these to the bite of any certain insect as questionable.

For full details of the extensive literature on the subject under consideration the reader is referred especially to the first mentioned article of Hecht, and to his later publications. It has not been the intention in this brief article to attempt any comprehensive bibliography.

SUMMARY AND CONCLUSIONS

The present study was undertaken in an effort to find effective treatment for certain extreme cases of sensitization to the stings of mosquitoes. It was evident from the previous exhaustive research of Hecht that the active substance of the salivary gland resided also in other tissues of the insect. In my experiments, therefore, the whole body served as the material for study.

There can be no reasonable doubt that the lesions described clinically in my four patients were due to the bites of mosquitoes. On repeated occasions the patient's arm, subjected to the sting of confined mosquitoes which had been hatched in my laboratory, developed typical immediate and delayed reactions, while normal controls, under the same conditions, showed no noteworthy deleterious effects. The hatching of mosquitoes in the laboratory, and subsequent feeding on banana or apple, also added the assurance that none of the insects used in my experiments had had a previous fill of blood.

The preparations used consisted of (a) simple buffered-saline extracts, (b) concentrated extracts by precipitation with ammonium sulphate, or, more often, cold alcohol or acetone. Both a and b gave strong specific reactions by intracutaneous inoculation in the sensitive patients and very little in the numerous normal controls. The concentrate gave uniformly larger reactions than the simple extract.

The preparations from males and females, young and old, reacted equally well on sensitive cases, with early wheals and later swollen erythematous areas of considerable size.

Reinoculation of extract from the same or another species of mosquito in a former site two or more days after the first inoculation showed abolition of the late reaction, but not of the early wheal. This raised the question of a possible multiplicity of antigens.

A relatively small number of injections desensitized three of the four patients treated, all of whom had been extremely reactive to the stings of mosquitoes. The antigen proved to be soluble in water and saline, specific for the host, nondialysable, and thermostabile. These qualities, together with its indiscriminate occurrence in the two sexes, and Hecht's demonstration of its distribution in various organs of the insect, pointed to some heat-resistant protein-bound antigen of the mosquito's body as the active principle.

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DISCUSSION

DR. MARION B. SULZBERGER, New York.—Dr. Benson's subject is important because of both theoretical and practical considerations. Even the ordinary wheal reaction to the bite of the mosquito is probably not due to the action of a secreted irritant but is probably in most instances attributable to an acquired and specific sensitization; that is, it is based on the same type of allergic mechanism as the ordinary wheals produced by the injection of the usual so-called protein allergens in the hypersensitive skin. This has been carefully studied and proved and there is a tremendous literature on the subject; the best summary is perhaps that by Otto Hecht.* Some investigators have gone to the trouble to let themselves be bitten hundreds of times on one area by bedbugs, in the attempt to produce local immunity to bedbug bites; and it was found that in some individuals such an immunity may be produced, in others not, even after hundreds of bites. The wheal type of reaction to certain insect bites has in some instances been shown to be accompanied by the formation of specific Prausnitz-Küstner antibodies, capable of transferring the specific wheal type sensitivity to skins not previously reacting to the bite of the particular insect concerned. On the other hand, the late papular twenty-four- to forty-eight-hour type of reaction is not accompanied by Prausnitz-Küstner antibodies. In studying the allergic nature of reactions to insect bites, there has been a huge amount of interesting work reported, mainly by entomologists. This is well worth reading both for the allergist and for the dermatologist. The workers in this field have come to the conclusion that most of the usual reactions to common insect bites are due to the production of an allergic hypersensitivity.

*Zentralbl. f. Haut- u. Geschlechtskr. **44**: 241, 1933.

Another interesting theoretical point in Dr. Benson's paper is that you can desensitize patients with comparative ease as far as the late twenty-four- to forty-eight-hour papular reactions are concerned; whereas the immediate or wheal type reactions, although also due to hypersensitivity, are extremely difficult to influence and usually remain constant in spite of all desensitizing procedures. We all see this paralleled in the treatment of hay fever and asthma, for the wheals are usually not much reduced, even after lengthy and successful treatment. I have often called attention to analogous phenomena observed in the course of tuberculin, trichophytin, and oidiomycin hyposensitization. We can reduce the twenty-four- to forty-eight-hour type reactions to these extracts with comparative regularity and ease, but if the patient once has a wheal reaction to tuberculin, or to trychophytin, or to monilia extracts, the wheal reaction stays as strong or almost as strong at the end of the hyposensitization period as it was at the very beginning. In other words, just as Dr. Benson reports in his work with mosquito allergen—the immediate wheal type reaction of skin hypersensitivity is most difficult to desensitize, while the late papular tuberculin type of hypersensitivity can usually be altered and reduced by specific treatment.

Dr. C. Malone Stroud, St. Louis.—In discussion of this paper, I wish to report briefly the history of a patient whom I saw first in December, 1934. Her chief complaint was urticaria, which was definitely made worse by mosquitoes. She knew that quinine and aspirin caused a rash. She did not feel that food was a factor in the production of urticaria. She was from a section of the country in which mosquitoes were very numerous; hence she had a considerable amount of discomfort from them. She stated that marked edema and generalized urticaria always followed a mosquito bite. She was markedly dermographic, and tests were of little value. Removal of suspected foods from her diet while she was at home had not afforded her relief. I obtained a large number of mosquitoes from her locality and made an extract of the whole mosquitoes. The extract was prepared as one would prepare meats. Intracutaneous tests with this extract showed a wheal with small pseudopods and considerable erythema. She was given three injections of this extract. I felt that this was insufficient therapy and that relief which came to this patient was due to the fact that she adhered strictly to a diet which was planned after many tests and many trial diets.

After returning home she had no urticaria when bitten by mosquitoes, unless, at the same time, she was eating foods to which she was sensitive.

I believe that Dr. Benson has made an important contribution to the knowledge of insect allergy.

Dr. Salvatore J. Parlato, Buffalo.—I think Dr. Benson is to be congratulated for bringing to us further information on the subject of insects and flies and their relation to allergic symptoms. I wish, however, to bring here a word of caution. Let us not be too enthusiastic, because we may make very serious mistakes.

Last year we had a very heavy mosquito season in Buffalo. Since the wife of my associate complained very bitterly of severe skin reaction from the bite, we studied the mosquito. We went a little farther than Dr. Benson. While we made no effort to separate the sexes, we confined our studies to the source of the injection material, namely, the head of the mosquito.

The female mosquito has salivary glands which produce a substance which is anticlotting. It is injected by means of a little proboscis. We, therefore, decapitated the mosquitoes, and made an extract of the heads, calculating we would include any allergenic substance in the salivary glands and the proboscis. The total protein content of this extract was quite high.

Testing a dozen nonallergic patients, one gave a positive reaction. I tested four multiple-sensitive patients, and all four gave positive reactions. Then I took a group of caddis-fly-positive patients, and two out of six gave positive reactions.

It occurred to me, as a result of these preliminary tests, that we may be dealing here with a nonspecific protein reaction. Dr. Benson stated that he made his extract from the whole mosquito. We must not lose track of the fact that the mosquito has serum, blood cells, and even excreta from the intestinal tract, whether it be a vegetarian or a carnivorous animal; and it is quite possible that delayed reactions which he speaks of may result from any of these factors.

I should like to ask Dr. Benson whether he carried on any controls on normal or nonallergic persons.

DR. BENSON.—I am familiar with the work of O. Hecht, and it is very valuable in those early effects.

The discussion of Dr. Parlato, of course, would not have been necessary if I had read my entire paper. There were ample normal controls, including everybody who worked in my office, and quite a few of the patients who were innocent victims, too, used as negative controls. We ran many times the number of negative controls that we did of the test cases.

I had intended, with the cooperation of the entomologists of the government, to get the probosces and, in fact, just the salivary glands. When I found that the harmless male gave material which reacted equally and similarly to that of the female, I realized we were not dealing with salivary secretion except so far as the salivary secretion carried with it the other products which have sensitizing qualities. The results cited furnish ample proof of specificity. We had strong positive reactions in our patients. We had practically no reactions in our controls.

HOUSE DUST HYPERSENSITIVITY IN PERENNIAL ASTHMA OF CHILDHOOD*

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SINCE Cooke's[1] original observations on the rôle of house dust as an antigenic factor in the production of asthma, the relative importance and the nature of this atopen have been discussed at considerable length in the literature.[2-19] Only one paper deals exclusively with children. Peshkin[16] reported 46 positive scratch tests to house dust in a series of 100 asthmatic children, and of these reactions he considered only half as being clinically significant. Table I shows the reported incidence of skin sensitivity to house dust in patients of all ages, as taken from the literature. It will be noted that this varies from 20 per cent to 96 per cent, depending upon whether the scratch or the intracutaneous method of testing is employed and also, no doubt, on the interpretation of the reactions and the methods of preparing the test extracts.

The present study was undertaken for three reasons: first, because of this wide variation in the accepted incidence of house dust hypersensitivity; second, because this atopen has not been thoroughly studied in relation to children; and third, because the well-recognized irritating quality of dust extracts in normal skin renders the interpretation of reactions difficult.

In a group of 71 children suffering from perennial asthma an effort has been made to correlate the degree of skin sensitivity to house dust extracts with the reagin content of the patients' serums.

METHOD

Material.—Seventy-one children were studied. These cases were selected only so far as pure seasonal pollen asthmatic persons were excluded. All suffered from perennial asthma, although in a few instances symptoms were aggravated during specific pollen seasons. The ages ranged from one to twelve years.

Dust Extracts.—Dust obtained by vacuum cleaner from upholstery, floors, and bedding from seven typical homes was collected and weighed. The dust was extracted twice with ether, each extraction lasting twenty-four hours. The ether was decanted and the dust spread out and allowed to dry on filter paper. The dried dust was then moistened and gradually stirred into Coca's alkaline extracting fluid[20] to the

*From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals.

amount of ten times the original weight of the dust. Extraction was permitted to continue for forty-eight hours at room temperature in a covered vessel. The material was then filtered through filter paper followed by Seitz filtration in order to sterilize the extract. It was bottled and cultured aerobically and anaerobically for sterility. The nitrogen determination by the Kjeldahl method was 0.26 mg. per c.c. The final product still contained a brown tinge. After it had stood for a few weeks in the ice box, a fine white precipitate settled out. This apparently had no deleterious effect, as skin reactions were unchanged before and after the appearance of the precipitate.

TABLE I

SUMMARY OF POSITIVE SKIN TESTS TO HOUSE DUST, TAKEN FROM THE LITERATURE

NO. OF PATIENTS	PER CENT POSITIVE TESTS	METHOD OF TESTING	AUTHOR
100	25	Intracutaneous?	Vander Veer,[14] 1921
327	33	Intracutaneous	Cooke,[1] 1922
100	47	Intracutaneous	Brown,[15] 1923
235	57	Intracutaneous	Meyer,[17] 1924
100 (Children)	46	Scratch	Peshkin,[16] 1926
162	42	Scratch	Rowe,[12] 1927
1,186	63	Intracutaneous	McLaughlin,[13] 1927
72	96	Intracutaneous	Munter,[19] 1928
1,250	20	Scratch	Rudolph and Cohen,[18] 1932
71 (Selected children)	79	Intracutaneous	Author's series, 1936

Method of Testing.—All 71 children were tested by the intracutaneous injection of approximately 0.01 c.c. of the stock dust extract on the middle of the flexor surface of the forearm. Twenty-seven gauge needles were used.

The reactions were read ten to twenty minutes after application and were classified as follows:

0—No wheal or erythema.

±—Wheal of 3 mm. diameter or less with smooth edges and small areola of erythema.

+—Wheal of 3 to 5 mm. with smooth edges and small areola of erythema.

++—Wheal of 5 to 7 mm. with slightly irregular edges and erythema of 20 to 30 mm.

+++—Wheal of 7 to 10 mm. diameter with definite pseudopods and erythema of 30 to 40 mm.

++++—Wheal greater than 10 mm. with definite pseudopods and wide erythema.

Passive Transfer.—Blood was taken by venipuncture from 26 of the 56 patients who gave two-plus or greater reactions. The parent accompanying the child, usually the mother, was used as the test sub-

ject. Two sites were prepared on the flexor surface of her left forearm by the intracutaneous injection of 0.2 c.c. of the patient's serum. Forty-eight to seventy-two hours later both these sites and two control sites on the corresponding areas of the right forearm were tested by the intracutaneous administration of approximately 0.01 c.c. of the stock house dust extract. An effort was made in each instance to inject slightly more of the extract into the control sites. The reactions were read and classified as noted above.

RESULTS

Table II gives the results of passive transfer in the 26 patients so tested. It will be noted that a one-plus reaction was frequently elicited in the control site on the parent. For this reason such reactions were

TABLE II

CHILDREN WITH PERENNIAL ASTHMA IN WHOM PASSIVE TRANSFER TO HOUSE DUST WAS DONE (FOR CLASSIFICATION OF REACTIONS, SEE TEXT)

PATIENT	AGE YR.	REACTION ON PATIENT	REACTION ON PARENT'S NORMAL SKIN	REACTION ON PREPARED SITE	INTERPRETATION
1. R. C.	6	+ +	+	+ +	Positive
2. F. D.	10	+ +	±	±	Negative
3. J. D.	5	+ +	±	+ +	Positive
4. M. K.	6	+ +	±	+ + +	Positive
5. J. K.	11	+ +	0	+ + +	Positive
6. M. O.	7	+ +	0	+ + +	Positive
7. D. W.	4	+ +	+	+	Negative
8. F. W.	10	+ +	±	+ +	Positive
9. W. T.	5	+ +	+	+ +	Positive
10. C. C.	7	+ + +	±	±	Negative
11. D. F.	7	+ + +	+ +	+ +	?
12. M. H.	11	+ + +	±	0	Negative
13. G. M.	9	+ + +	0	+ + +	Positive
14. F. S.	6	+ + +	+	+ +	Positive
15. P. L.	8	+ + +	0	+ + +	Positive
16. S. K.	8	+ + +	0	+ + +	Positive
17. N. K.	6	+ + +	±	+ + +	Positive
18. L. B.	5	+ + +	0	+ + +	Positive
19. R. M.	11	+ + +	0	+ + +	Positive
20. E. T.	11	+ + +	+	+ + +	Positive
21. J. D.	6	+ + +	+	+ + +	Positive
22. E. D.	4	+ + + +	+	+	Negative
23. G. F.	12	+ + + +	±	+ + + +	Positive
24. M. Q.	11	+ + + +	0	+ + +	Positive
25. W. W.	9	+ + + +	+ + + +	+ + + +	Positive by therapeutic test
26. R. V.	10	+ + + +	±	+ + + +	Positive

SUMMARY

NUMBER OF PATIENTS	REACTION ON PATIENTS	NUMBER OF POSITIVE PASSIVE TRANSFERS	PER CENT POSITIVE PASSIVE TRANSFERS
9	+ +	7	77
11 (+1?)	+ + +	9 (+1?)	82
5	+ + + +	4	80
Total 25		20	80

considered to be irritative and not indicative of a specific sensitivity. The differences between a one-plus reaction in the control site and a two-plus reaction on the prepared site was considered significant. A striking example of the correctness of this interpretation was presented by Patient 1 (R. C.) in whom three general reactions were produced on three occasions by injecting more than 0.1 c.c. of the dust extract subcutaneously, proving conclusively that the two-plus skin reaction on her own skin and at the site of passive sensitization was clinically significant.

Two test subjects exhibited control reactions greater than one-plus and of the same intensity as in the prepared sites. In the first instance, Patient 11 (D. F.), there is no evidence other than the two-plus skin test to suggest whether or not the patient was sensitive to house dust, and so this case is considered questionable and recorded as such in the summary of Table II. In the second instance, Patient 25 (W. W.), the test subject gave the history of rhinorrhea and sneezing when she dusted. The patient also proved to be hypersensitive as evidenced by the complete cessation of his asthmatic attacks following a course of house dust injections. This patient is therefore included among those exhibiting a positive passive transfer test in the summary.

One factor of considerable interest is the parallelism between the degree of the reaction in the patient's skin and the reagin content of his serum as evidenced by the severity of the reaction in the prepared site on the test subject. For example, of the 12 patients exhibiting a three-plus skin reaction to house dust extract, there were nine positive passive transfers, of which eight were three-plus.

From the summary of Table II it will be seen that 77 per cent of the patients exhibiting two-plus skin tests, 82 per cent with three-plus tests, and 80 per cent with four-plus tests showed positive passive transfers. Since Coca[21] has shown that approximately 85 per cent of nonatopic individuals have the capacity of fixing reagins in their skins and hence are capable of receiving a passive transfer, it may be assumed that most, if not all, of the failures to exhibit reagins were due to the inability of the test subject to fix the reagins. It may therefore be concluded that practically all two-plus or greater intracutaneous tests with this house dust extract in children are significant so far as they indicate the presence of reagins.

Analyzing the entire group of 71 children suffering from perennial asthma in relation to their ages and the degree of skin reaction to house dust extract, the following result was obtained:

NUMBER OF PATIENTS	DEGREE OF SKIN REACTION	AVERAGE AGE
15	0, ±, +	5.1
23	+ +	6.0
25	+ + +	7.8
8	+ + + +	9.5

The plus or minus and one-plus reactions were considered irritative phenomena and of questionable or no significance so far as specific hypersensitivity is concerned. Two facts are brought out. First, considering two-plus or greater reactions positive, which conclusion seems justifiable from the results of the passive transfer experiments, 79 per cent of all children between one and twelve years of age suffering from perennial asthma are skin and serum hypersensitive to house dust. Second, the frequency of house dust hypersensitivity and the degree of this hypersensitivity as evidenced by skin tests and reagins increases with advancing years.

DISCUSSION

In comparison with the percentage of house dust sensitive cases as reported in the literature (Table I), this series of children shows a strikingly high incidence of dust sensitivity, namely 79 per cent. The explanation probably is that the cases under discussion are all non-seasonal in character, whereas those reported in the literature are for the most part all classes of respiratory allergy, including pollinosis.

Cooke's[1] contention that the atopen in house dust is independent of other known allergens is borne out in this series. No correlation between the dust reactions and those of other inhalants, pollens, or foods was observed.

Only two of the 56 dust sensitive children failed to react to at least one other substance, and, as a rule, many reactions were elicited by either the scratch or the intracutaneous technic. The complexity of this multiple sensitivity makes an evaluation of the importance of house dust as a clinical cause for asthma very difficult. This is especially true of children, who do not present a long history of symptoms and whose attacks cannot be satisfactorily correlated with place, because their environments are relatively uniform. The increasing frequency and magnitude of the skin reactivity with advancing years suggest, however, the acquisition of a clinical sensitivity with prolonged contact. The importance of inhalants in general as causes of respiratory allergy with the advancing years of childhood has already been pointed out by Stuart.[22]

Finally, accumulated experience has shown that those substances with which human beings have the most intimate and prolonged contact are the substances which are most frequently to blame for the causation of human allergies. For this reason the ubiquitous house dust should logically be an important factor in the production of allergic respiratory symptoms.

SUMMARY

By means of intracutaneous tests and passive transfers it has been determined that approximately 79 per cent of children between the ages of one and twelve years who suffer from perennial asthma are

skin sensitive to house dust extract and have reagins to this atopen in their serums. The frequency and severity of this sensitivity as evidenced by the magnitude of the skin test and passive transfer reaction increase with the advancing years of childhood.

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ROENTGEN TREATMENT OF SEVERE ASTHMA*

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WHILE the treatment of patients with periodic asthma is usually quite satisfactory, workers in the field of allergy have noted that in any large series of patients with asthma a certain number fail to respond to the usual treatment based on the allergic findings or to nonspecific treatment as it is usually employed.

The patients in the present study suffered from frequent daily attacks of asthma from which they obtained but slight temporary relief by using epinephrine and other antiasthmatic remedies. Positive skin tests may or may not have been found, and specific allergic treatment failed to bring relief. Most of these patients had had asthma for many years, often beginning with a frank, periodic pollen asthma, or they may have had asthmatic attacks only with winter colds or on exposure to animal danders. The attacks gradually became more severe, occurred more often, and lasted longer until the patient had them daily and was completely incapacitated. Specific sensitiveness gradually became less important, and nonspecific factors predominated in the production of attacks. Treatment by specific allergic methods failed, even in those cases in which good results had been obtained in former years. The symptoms then gradually became more severe and finally in some cases intractable asthma developed.

The use of roentgen rays in the treatment of patients with asthma is not new, and most investigators have observed beneficial effects from such treatment. Various areas, such as the thorax, spleen, bones, and even the pituitary gland, have been irradiated with essentially the same effect. In 1931 roentgen treatment was advised for a patient who had received little benefit from the usual methods of treatment. Complete relief of symptoms followed, and, thereafter, with each recurrence of asthma he returned for further roentgen treatment, with the results shown in Table I (Case 1). Twenty-three patients with very severe asthma who were not relieved by other measures have been treated with roentgen rays since then (Table I).

It needs but a cursory survey of the literature on roentgen therapy of asthma to convince one that the conceptions on which this treatment is based are as empirical and as indefinite as is our knowledge of the true nature of asthma. As has been said, one can find reports of cases in which the pituitary body, spleen, liver, suprarenal glands, or the pancreas

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have been irradiated with success almost as frequently as in reports of those technics which make a more direct attack on the pathologic process in the thorax. In this series the following areas have been irradiated as indicated on the table, anterior mediastinal (A), splenic (S), and paravertebral (P), alone or in combination. Success and failure were obtained with each. We have favored irradiation of the mediastinum through two paravertebral fields as this method, in general, seemed to give less gastrointestinal reaction than did the anterior-posterior cross fire. It is possible, however, that somewhat better results were obtained when the anterior mediastinum was irradiated in addition to the paravertebral fields.

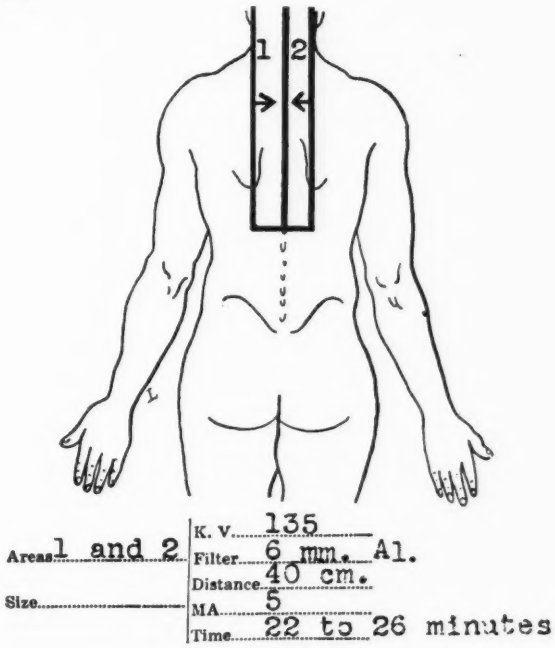

Fig. 1.—The technic ordinarily used.

Fig. 1 illustrates the scheme of irradiation now used and its technical factors. Unless some contraindication exists, and provided the patient can lie prone without undue discomfort, the treatment is completed in one session. Otherwise, one-half the dose is given on successive days.

For about two to six hours after irradiation the patient commonly complains of slight headache, lassitude, and apathy, but rarely of nausea or vomiting. A few patients complain of pain over the back for one or two days, and an occasional patient may have a more marked asthmatic attack than is customary for a short time after treatment. As a rule, real improvement is noticed within a day or so. Cough, expectoration, wheezing, and dyspnea decrease and sometimes disappear entirely within the next two weeks. As long as the condition of the patient has improved,

TABLE I

RESULTS OF ROENTGEN TREATMENT OF 23 PATIENTS WITH SEVERE ASTHMA

CASE	AGE, YEARS	DURATION OF ASTHMA			DATE OF TREATMENT	RELIEF OBTAINED, PER CENT	DURATION OF RELIEF	SKIN TESTS	AREA TREATED	FAILURE OF TREATMENT
		TOTAL, YEARS	SEVERE	INTRACTABLE						
1	26	21	Few weeks		7/ 6/31	100	5 months	Neg.	A and P	
					12/31/31	100	16 months		P	
					4/21/33	100	6 months		P	
					11/14/33	100	8 months		P	
					7/25/34	100	6 months		P	
					2/ 5/35	100			P	
2	52	19	Each winter 10 years		10/22/32	90 to 100	14 months	Neg.	P	
					12/12/33	90 to 100	To date		P	
3	58	9	4 years	3 months	11/18/32	0 (worse)	0	Neg.	A and S	x
4	50	8	6 weeks		3/14/33	"Considerable"	2 weeks	?	P	
					4/13/33	"Definite"	6 weeks		P	
					6/12/33	"Not much"	0		S	x
5	19	15	2 months	2 months	10/12/33	0 to 25	2 months	Pos.	P	x
6	30	2	2 years		4/13/33	50	1 month	Neg.	P	
					6/11/33	50 to 75	1 month		A and S	
					7/18/33				A and S	
					8/ 8/33	0 to 25			A and S	
7	46	2	1 year		1/17/34	25 to 50	Few days	Pos.	P	
					7/ 4/34	25 to 50			P	x
8	66	4	1 year		3/ 9/34	90	To date	Neg.	P	
9	50	1	4 months		5/ 5/34	0		Neg.	P	x
10	76	?	9 months		6/ 1/34	100	To date	Neg.	A and P	
11	48	Many	2 months	3 weeks	10/10/34	75	3 to 4 weeks	?	P	

TABLE I—CONT'D

CASE	AGE, YEARS	DURATION OF ASTHMA			DATE OF TREATMENT	RELIEF OBTAINED, PER CENT	DURATION OF RELIEF	SKIN TESTS	AREA TREATED	FAILURE OF TREATMENT
		TOTAL, YEARS	SEVERE	INTRACTABLE						
12	36	Many	2 years	6 months	10/18/34	25	2 weeks	0	P	x
13	27	15	10 years	5 months	7/31/34			Neg.	A and P	
					8/14/34				A and P	
					9/19/34	60	2 months		A and P	
14	43	1	3 months		9/21/34			Neg.	A and P	
					11/19/34	50	2 months		A and P	
15	48	2	2 years		10/19/34	0		Neg.	A, P and S	
					11/ 5/34	25			A, P and S	
					12/ 6/34	100	To date		A, P and S	
16	43	2			10/19/34	0	0	Neg.	P	x
17	61	6	1 year		10/27/34	25	10 days	Neg.	P	x
18	50	1½	14 months		10/20/34	98	6 weeks	Neg.	P	
19	52	3	2 years	3 weeks	10/31/34		3 weeks	Neg.	P	
					12/ 3/34	100	3 weeks		A and P	
20	49	2	2 years		10/22/34	0		Neg.	P	x
21	48	12	12 years		11/ 2/34	75 to 100	3 weeks	Neg.	P	
22	32	16	3 years		11/15/34	75	1 month	Neg.	A and P	
23	56	8	1 month		1/ 4/35	0	0	Pos.	P	x

A—Anterior.
P—Posterior (paravertebral).
S—Spleen.
X—Complicated by addiction to morphine.

we prefer to withhold further treatment, but as soon as any of the warning signs appear, which the patient has learned mean a return of his attacks, further treatment may be given. As can be seen from the table, the degree and duration of improvement vary among different patients. Since there is practically no risk whatever of producing damage to the skin or the thoracic structures with the doses of roentgen rays we commonly use, there is no contraindication to repeating roentgen treatments several times at intervals of about a month.

The advantages of the treatment as we have outlined it are that it is technically easy to administer, and it is well tolerated by the patient.

Although the underlying mechanism by which the beneficial effects of roentgen therapy is produced is unknown, it would seem from the review of Desjardins[1] that roentgen rays produce a decrease in the secretory power of the mucous glands in the trachea, liberate antibodies by destruction of leucocytes, and may have a stimulative effect on the production of eosinophiles.

SUMMARY

Twenty-three patients were treated, their average age being forty-six years. The average duration of the asthma was seven years, and the average duration of the severe asthma was one and a half years.

In five of 23 patients, 21.8 per cent (Cases 1, 2, 8, 10, and 15), marked and satisfactory relief lasting many months was obtained. In eight other patients, 35.0 per cent (Cases 6, 11, 13, 14, 18, 19, 21, and 22), from 50 to 75 per cent relief lasting from three weeks to as long as two months was secured. The remaining 10 cases, 43.5 per cent, are classed as failures since less than 25 per cent relief was obtained or, as in two cases (7 and 11), while more relief was obtained, it was of very short duration.

Roentgen therapy in some cases seems to be of definite benefit in interrupting the cycle of attacks, and the usual methods of treatment again become effective. In those obtaining relief the usual allergic factors must still be considered. Although the percentage of failures is high, it should be remembered that in this group roentgen therapy was used only when other measures had failed to relieve symptoms.

We believe that our results with roentgen therapy in patients suffering with severe asthma warrant its consideration in the symptomatic treatment of such patients.

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Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

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Rest as an Aid in the Management of Certain Allergic Diseases. Barney A. Credille, M.D., Flint, Mich. (Abstract.)

More emphasis should be placed on the importance of fatigue and exhaustion as a vital secondary factor in certain allergic diseases. Unquestionably, fatigue has been instrumental in precipitating the initial attack in some cases.

An allergic patient has a definite threshold of tolerance in regard to fatigue. When this is lowered, the specific and nonspecific agents precipitate an attack. It has been stated that sitting quietly in a chair raises the energy requirement of the body 20 per cent over that needed when reclining. Allergic paroxysms must therefore make far greater demands on the patient's energy.

Prolonged rest has been found a valuable adjunct to the conventional forms of treatment of asthma; in allergic disorders complicated by cardiac involvement, emphysema, and bronchitis; and in patients who are nervous, feeble, and undernourished. A hospital is the ideal place for complete rest.

It is thought that the improvement in asthma following an extended illness, such as an infection or accident, may be attributed to the coincident rest.

Eczematoid Dermatoses Due to Hypovitaminosis With Secondary Food Sensitization.* Cleveland White, M.D., Chicago, Ill. (Abstract.)

During the past three years, eleven patients with recurrent eczemoid patches and plaques on the ankles have been observed. These patches were circumscribed, usually erythematous, occasionally vesicular; beginning occasionally on one ankle but far more often on both, symmetrically placed. The lesions at times disappeared completely, especially during the summer months. Subjective symptoms ranged from mild pruritus to severe, almost intolerable burning. Some patients had recurrent attacks for three years, others as long as nine. There were nine males and two females whose ages varied from twenty-eight to fifty-seven years. All patients gave a history of having extreme photosensitivity of the skin, and direct sunlight had to be avoided.

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Elimination of foods to which positive skin reactions by the scratch method had been obtained led to some improvement, and ingesting such foods induced aggravation of the lesions. The patches, however, persisted despite such eliminations. It was then ascertained that most of the patients ate very sparingly of vegetables, especially the leafy ones. By adding these to the diet as well as vitamin products (e.g., cevitamic acid), the lesions vanished. Likewise the evident food sensitization present disappeared as the vitamin deficiency state was corrected. It is thus apparent that borderline vitamin deficiency diseases do occur, in spite of the belief that the American diet is, in general, well balanced.

DISCUSSION

Dr. Milton B. Cohen, Cleveland.—I do not think this paper should be passed by without considerable discussion. It is very interesting, as one listens to the papers this morning, to note how as allergists we are beginning to concern ourselves with much more widespread conditions in sick people than we used to, and I believe that this is a very important point of view for us to maintain.

There are several points about vitamins in relation to allergy and in relation to such a syndrome as Dr. White described, which interest me very much. It seems to me that there are two general points of view that one has to keep in mind in considering this subject:

First, there may be, as he describes, a general hypovitaminosis due to the fact that the patient simply does not get enough vitamin intake and, therefore, is predisposed to many things because he is below par.

The other aspect is that we are prepared to say now quite definitely, though we are not ready for publication, as result of our association with Dr. Todd, in Cleveland, that the individual who has active allergy is a poor utilizer of all the vitamins and of practically everything you put into him. He does not use his minerals well, or his vitamins well, so that no matter how much you give him, there is poor utilization of what you might call the maximal amount you offer him; whereas the normal individual, given even a reasonable amount, gets more utilization.

Dr. George L. Lanbright, Cleveland.—I should like to inquire whether the doctor pursued his studies further to determine whether all the articles were eliminated in these neurodermatitis cases to which the patient was sensitive. In other words, to ascertain whether he could not get rid of these dermatoid conditions by dietary elimination alone without adding the additional factor of a vitamin deficiency. We have had singularly good results in most all of our cases by dietary elimination alone based on skin reactions and leucopenic index studies.

Dr. John H. Mitchell, Columbus.—Dr. White, in describing this lesion, specified specifically the ankle lesion. We also see these lesions on the dorsum of the hand, and they seem to be identical with those that occur on the lateral surface of the ankle—sometimes on the dorsum of the hand alone. I wonder whether this régime has been utilized in lesions of the dorsum of the hand which are in some quarters designated as dyshidrosis.

DR. C. MALONE STROUD, St. Louis.—I should like to ask Dr. White whether sunshine predisposes to the occurrence of the lesions which he describes. It seems that sunshine favors the production of dermatitis in pellagra, which, as we know, is connected somewhat with avitaminosis.

DR. WHITE.—I wish to thank Dr. Cohen particularly for the points brought up in his discussion. I certainly believe that the vitamins do have a place as etiologic agents in certain dermatoses. I am enlightened by his information that allergic patients may be poor utilizers of vitamins. In this particular syndrome which I have just discussed, I have found it to be a very stubborn affair, and I did not find any information on it in the literature or in the textbooks except coming under the hackneyed term of eczema.

As far as the elimination of foods is concerned, I have endeavored to carry that out both by elimination diets and by the results of food tests. In a few instances I have secured good results. As one discusser has brought out, the dermatoses are due to foods in some cases. However, in a large percentage of cases in which I acquired complete elimination of the suspicious food, a complete clinical cure was not secured.

Whether they should be classed under the term neurodermatitis is a moot question at the present time. I believe there is a tendency now among dermatologists not to use the term neurodermatitis, because of the rather marked difficulty of determining just what comes under that heading.

As to clinical findings, while the patient may not show the gross findings of hypovitaminosis, as scurvy for instance, there is a lack of utilization of some of the vitamins.

As to lesions on the backs of the hands which one discusser brought forward, I believe that such a clinical syndrome can occur there as well as on the ankles. That will take further study, however, and I would not want to express a definite opinion at the present time. On the palms there are lesions resulting from dyshidrosis which may be associated with fungus infection elsewhere.

Allergic Symptoms in the Psychiatric Patient. KATHARINE BAYLIS MACINNIS, M.D., Binghamton, N. Y. (Abstract.)

Statistics available at present seem to show that one person in seven is allergic at some time during life. This number is increasing yearly as: more individuals with mild or infrequent symptoms apply to physicians for treatment; allergic tendencies are inherited; diagnostic methods are becoming more accurate; and some diseases not considered allergic are now known to be included under that classification.

Assuming this to be true among the so-called normal population, the question of the prevalence of allergic manifestations among the psychotic was raised, and it was concluded that a study of allergic patients at state hospitals for the insane offered an excellent opportunity

for considering a large number of allergic persons from a symptom standpoint only. No tests were made at this time.

Since it is a well-established fact that a positive skin reaction does not mean that the individual tested is allergic at that moment to that particular allergen, but may merely mean that such an individual is potentially allergic, it was therefore felt that a study of the type of allergic reactions occurring among psychotic patients would be of considerable interest and possibly of some value. It is well to state now that only frankly psychotic patients are being used in this paper. No patient with any type of neurosis is considered.

Two institutions, one in Columbia, South Carolina, and one in Binghamton, New York, were selected for a preliminary study which would precede the detailed study, now in process, of a definite group. Each institution numbered more than 3,500 patients. Therefore, assuming allergic reactions to appear as among the population at large, one should have found at least 1,000 patients to study. It might be expected that histories taken on psychiatric patients would be lacking in the details necessary to an allergic study; nevertheless one would anticipate allergic manifestation to be frequent—probably constant in many instances—among the inmates. It was learned, however, with considerable surprise, from the pathologist of the Binghamton State Hospital, that but five cases of asthma had appeared in the last five years, and the hospital in Columbia denied having any patients with allergic disease.

Three of the five cases gave no history of attacks during the mental illness, but upon a return to a mental balance showed definite manifestations of allergic conditions.

The problem, then, may be stated simply: Why do not more psychotic patients show symptoms of allergic disease? What change takes place which suppresses allergic symptoms when a psychosis develops, and how is the reverse brought about which permits a return of allergic disturbances as a normal state is approached in the mental condition?

An allergic disease cannot be said to immunize one from a mental illness, and yet there seems to be a temporary immunization from allergic symptoms during the course of the more severe mental (dementia precox) and emotional (manic-depressive) diseases. One cannot safely use the term immunity, and one hesitates to assign the transient changes to chemistry or a physiologic transposition, but unquestionably there is a fundamental reason for this striking change which thus far is not explained. It is admitted that allergic patients placed in hospitals which are reasonably free from dust are benefited; yet this factor does not explain the absence of allergic manifestations in psychotic patients. Up to the present the literature gives little that deals with the problem concretely.

CONCLUSIONS

1. A survey of more than 7,000 psychiatric patients revealed five, or 0.07 per cent, with allergic symptoms.

2. Three of these showed loss of or improvement in allergic symptoms while suffering from a mental illness, and return of allergic symptoms upon an approach to mental balance.

3. The cause of this low percentage of psychiatric patients with allergic disease is unknown.

SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

ATLANTIC CITY, N. J., MAY 2, 1936

Local Allergy of the Eye. SAMUEL J. TAUB, M.D., Chicago, Ill. (Abstract.)

Vernal conjunctivitis has been recognized by ophthalmologists as manifestations of allergy. Lehrfeld[1] reported a group of 87 cases of vernal conjunctivitis and stated that this condition is a manifestation of allergy. Tooker[2] observed that the ingestion of certain foods produced an exaggeration of the eye symptoms in cases of tuberculous keratitis. Parlato[3] saw a patient with corneal ulcers, who was definitely sensitive to orris root and several foods. Upon the removal of orris root and certain positive foods a complete recovery occurred.

The association of a seasonal conjunctivitis with pollen is very definite. Many of our hay fever patients have a preponderance of local eye symptoms and minor symptoms in the respiratory tract.

The perennial cases of chronic conjunctivitis are usually treated for long periods of time, and, when they do not respond to local treatment, the help of the allergist is sought. The importance of recognizing these cases early becomes apparent when one realizes that more serious corneal ulcers and impairment of vision may result if the hypersensitiveness in many cases of chronic conjunctivitis is not recognized, as Parlato has so well demonstrated.

CASE REPORT

Mrs. N. H., aged forty-two years, proprietor of a dress shop, was referred on Oct. 23, 1935, by an ophthalmologist who requested an allergic study because of a chronic conjunctivitis in both eyes. The patient complained of an itching, burning and sandy feeling in both eyes for a period of four years. These symptoms were present all year around, and the patient thought she felt worse while in the dress shop and better while at home or away from the shop. A year ago while on a vacation for four weeks, the symptoms improved and the eyes felt almost normal. Upon her return to her business a recurrence of symptoms followed. One brother has hay fever.

The physical examination was negative except for a bilateral redness of the conjunctivae of both eyes, corneal and palpebral and a watery thin secretion. A smear of this secretion showed a few eosinophiles and no pus cells. Complete skin tests were made with various tree, grass and weed pollens, dust, epidermals, foods, orris root and other miscellaneous proteins, and a positive reaction occurred with silk only. The cutaneous test with powdered silk and the intradermal test with 1:1,000 silk extract both yielded a positive reaction within ten minutes. Patch tests were done with samples of silk obtained from dresses in the patients shop and negative reactions resulted. Patch tests were also done with petrolatum, cold cream, various cosmetics, perfume and a paraphenylendiamine dye, all with negative results. Because of the irritation of the eyes it was not deemed advisable to attempt to drop silk extract in the conjunctiva.

The patient was instructed to avoid handling silk dresses and to wear wool instead of silk clothing. She was also advised to spend as little time as possible in her store for the time being. A rapid improvement occurred. Within a period of four weeks the itching and burning stopped and the redness of the conjunctiva diminished. Two months later, the eyes appeared perfectly normal. Desensitization by subcutaneous injections of a silk extract was carried out because of her unavoidable contact to silk from other sources.

The cocoon of the silkworm is composed of two proteins, a fibroin which is insoluble in water and a sericin (silk gum or glue) which is soluble in water and somewhat volatile. The silk gum or glue present in raw silk amounts to 24 per cent to 26 per cent. While this silk gum is removed to a considerable extent in the finer grades of silk dresses, it is purposely left in the cheaper grades of silk dresses in order to give the material a gloss and a more compact feel. The inhalation of this volatile silk gum or glue which reaches the conjunctiva by way of the nose and tear ducts, thence into the conjunctival sacs, is responsible for the irritation in the eyes.

In a previous article[4] it was shown that the inhalation of silk protein through the respiratory tract is responsible for atopic eczema, perennial rhinitis and asthma, and we were able to demonstrate local nasal mucosa irritation after instilling silk extract into the nose.

Sulzberger and Vaughan[5] went a step further and demonstrated a positive passive transfer to silk in atopic dermatitis after inhalation of the protein. Within eighteen minutes after blowing powdered silk protein into the nose a positive reaction occurred at the site of the passive transfer. These authors emphasize the importance of inhalants and the respiratory route of absorption of proteins in the study of many allergic conditions such as atopic dermatitis, urticaria, prurigo mitis, infantile eczema and even some types of contact dermatitis.

SUMMARY

A case of chronic conjunctivitis is cited the cause of which was found to be a hypersensitiveness to silk.

Removal of contact to silk and specific desensitization resulted in a cure.

The importance of recognizing hypersensitiveness in many cases of chronic conjunctivitis is emphasized in order to avoid more serious eye complications.

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Use of Adrenal Cortical Hormone in Treatment of Allergic Manifestations. HARRY B. WILMER, M.D., and MERLE M. MILLER, M.D., Philadelphia, Pa. (Abstract.)

Both in adrenalectomized animals and in Addison's disease, there are many symptoms which allergic individuals of a certain type show, particularly asthenia with marked vasomotor instability and collapse. Laboratory tests, with the possible exception of altered carbohydrate metabolism, so far have not proved definite adrenal insufficiency in allergy, but from the clinical standpoint there is lack of medullary substance and possibly also of cortical matter.

With this in mind, selected cases of allergy presenting some resemblance to a moderate hypoadrenia were injected parenterally with adrenal cortical hormone prepared by the method of Swingle and Pfiffner. Seventy-two patients who had been refractory to other therapeutic measures were given intramuscular injections of the hormone. The details of diagnosis and treatment of 15 cases are presented in this report, together with a summary of the results obtained. Of this group, five patients secured complete relief of symptoms and a marked increase in general resistance. Only partial relief was experienced in the next five, and no relief in the third five. These patients were thoroughly worked up in respect to classification of allergy, such as extrinsic or intrinsic factors, history, laboratory data, etc.

The dose of cortical hormone varied from 1 c.c. to 4 c.c., and the total amount given was from 20 c.c. to 80 c.c. The interval between injections ranged from twenty-four hours to one week, depending upon the patient's condition and indications for increase and decrease of maintenance dosage.

No significant change in blood pressure was noted, except that in patients with a marked hypotension it increased with the gain in general resistance. A gradual marked increase in weight was noticed in thin asthenic patients. In the majority of cases there was a definite marked progressive improvement in general health.

CONCLUSION

Seventy-two patients were treated with cortical hormone, 90 per cent of whom were refractory to other methods. In 42 per cent an improvement in the general condition was noticed. In the thin asthenic individual 80 per cent increased in weight; in the other type of patient there was no significant change. There was no significant change in sugar tolerance, and blood pressure readings varied but little. There was no alteration of blood chemistry. Complete relief was obtained in 10 individuals or 13 per cent, partial relief in 21 or 29 per cent, and no relief in 41 patients or 58 per cent of those treated.

DISCUSSION

DR. MILTON B. COHEN, Cleveland.—This is a very difficult paper to discuss because it brings up so many controversial topics. I have been fortunate in having lived through a good deal of the controversy on the adrenal cortical hormone, being a very close friend of one of the people involved in it.

When we quote results in animals with any extract we are up against quite a problem. We do not know where we stand. Toxic elements have been shown to be present in many of these extracts. You do not know, therefore, what you are injecting.

May I ask, did you give salt to these people?

DR. WILMER.—Not to this group we are now talking of.

DR. COHEN.—If you did, that would account for the fluctuations in weight.

I believe you get nowhere with reporting clinical impressions no matter how good. Somebody has to take this problem to the laboratory. We should create standard control conditions and show that we can control some of the induced types of allergic reactions. Then we will have a background for our work.

It is well known—and I am not saying this to be hypercritical, and I hope you will take it in the spirit in which it is offered—if an asthmatic person changes doctors, he improves. There are a great many things about the asthmatic that we do not know. You cannot follow a case two months or three months and say that you have obtained a result. What is going to happen to these people after your supply runs out? How long are you going to keep them on these supplies? What periods of remission did they have during the twelve months preceding the present treatment? Did they ever go for two months before without an attack of asthma? It is probable that they did. You always have a group of people to whom you give something and they do not have another attack from that time on.

I remember one woman to whom I gave injections of a colon bacillus vaccine, and during the year I knew her she did not have an attack. The asthma disappeared after the first dose. If I had given her cortical adrenal extract, the result would have been attributed to it.

I say these things merely to point out that we cannot judge entirely on clinical impressions. Thirteen per cent good results is not

enough to justify the feeling that the result necessarily can be related to the cortical adrenal extract with which the patients were treated.

DR. LESLIE N. GAY, Baltimore.—Were these patients constantly in the hospital? Then, as Dr. Cohen has just said, I think it is well recognized that in adrenal deficiency large doses of salt make it quite unnecessary to give cortical hormone. If Dr. Wilmer has failed to treat a group of asthmatic patients with a high salt diet, I rather feel that the most important control has been omitted, and therefore conclusions from the use of cortical hormone cannot be definitely reached.

DR. A. H. FINEMAN, New York City.—In 1931 I first used the adrenal cortical hormone in the treatment of bronchial asthma and reported the results in 1933, in the March issue of the JOURNAL OF ALLERGY. Four cases of severe and protracted asthma, which did not respond to any other form of therapy, were selected for the study. They had been under observation for from six months to two years. Three were protein sensitive and one was non-sensitive by skin tests.

The results obtained with the cortical hormone were as follows: one patient showed marked improvement, one moderate, one slight, and one no improvement. In all cases, however, there was a definite increase in appetite, strength, and weight, and the general condition of the patients was much improved.

The suprarenal cortex extract was administered subcutaneously and intramuscularly, beginning with a dosage of 0.5 c.c. and gradually increasing to 4.0 c.c. per dose. Injections were given three to four times weekly over a period of from two to four months each.

At that time I held no extraordinary claims for the suprarenal cortex extract in bronchial asthma but merely reported the results obtained in a small series of cases. So far as the results of Dr. Wilmer are concerned, I see no greater incidence of improvement in his cases.

Now Dr. Wilmer reported on 76 cases and discussed in detail 15 of those more fully treated. Five of the fifteen showed good results, five poor, and five no results. Only 13 per cent of the entire series showed marked improvement. As Dr. Milton Cohen stated in his discussion, this is a small percentage of satisfactory results in dealing with asthmatic individuals, when so many factors must be taken into account.

In 1935 Dr. Milton Cohen reported a series of four patients treated with cortical hormone with no improvement in asthma. He made no study of the general condition of the patients. In the same year Pottenger and his associates reported on the administration of cortical extract by mouth with the addition of salt and obtained favorable results.

We must be very careful in drawing conclusions from any series of cases studied over a short period of time. A more critical evaluation of cortical hormone therapy in asthma can better be gained by a study of cases treated over a prolonged period of time with dosage increased up to 10 c.c. In my work no untoward reactions occurred, and I consider it safe to use the larger dosage.

DR. MARION B. SULZBERGER, New York City.—I cannot report a long experience with the use of cortical hormone, but Dr. Wilmer and Dr. Miller have mentioned the effect in neurodermatitis, or to use a better

name, atopic dermatitis. I should like to bring out some characteristics of this atopic dermatitis which may have some bearing on the problem under discussion.

Unfortunately, I see a great many of these cases. I say unfortunately because some of the long-standing inveterate cases coming to my office prove to be refractory to any present methods of treatment. First, dermatologists have long recognized the fact that these patients are sometimes underweight, and that as a group they are certainly not obese. Very rarely, if ever, is this dermatosis encountered in a stout individual.

Second, one has been struck for a great many years by the fact that these patients have a tendency to brownish gray hyperpigmentation of the skin. Not only the areas that are scratched and irritated, but often the entire skin takes on a dirty brownish gray hue. Both these facts have some relationship to the question of adrenal cortex insufficiency.

I cannot record more than an imperfect impression of the effects of treatment of atopic dermatitis with extracts of adrenal cortex. I have employed "eschotin," which may be much weaker than the preparations used by the present authors. By the daily injection of 2.0 c.c. I have temporarily helped relieve the itching and produced some alleviation of the skin manifestations in four severe intractable cases of atopic dermatitis. However, the process returned to its original state when the injections were stopped. In a fifth, a deplorably severe case, accompanied by atopic cataract of both eyes, the "eschotin" injections exercised no beneficial effect whatsoever on the skin or on the eye manifestations.

Dr. Royce Paddock, Newark.—I should like to ask Dr. Wilmer the amount of carbohydrate that he used, and whether these patients had been on a high carbohydrate diet previous to the test?

Dr. Robert A. Cooke, New York City.—I should like to ask Dr. Wilmer what percentages of the skin sensitive allergic cases that he has studied show what he considers to be the low sugar tolerance curve?

Dr. Wilmer.—I thoroughly agree with Dr. Cohen's response to this presentation. This paper as presented is a review of a number of cases treated with cortical hormone, and the results obtained. They are cases that have been absolutely refractory to all other treatment.

There seems to be a definite criticism that we can show only 13 per cent cured of the series presented, but I feel that this is an addition to our armamentarium, because these cases cured would most certainly have remained in the class of advanced convalescence if they had not been treated by this method. It must be remembered also that the series of cases relieved might have shown better results if we could have had a chance to have had them under treatment a longer time.

The question of comparison between the cortical hormone and eschotin has been asked. In Dr. Swingle's laboratory eschotin has been shown to be ten times weaker than the preparation prepared by Dr. Swingle.

We use 1.5 grams of sugar per kilo body weight, and use the Folin method.

Dr. Gay asks whether we had used salt in any of these cases. We did not. The cortical hormone was used alone; no other method of treatment was used. The individual was allowed to go at will, following his own dictate as far as possible, our idea being to try to find out whether the cortical hormone was giving the result, and not complicating the issue by any other method of treatment, rest or otherwise.

The question has been asked—were these patients hospitalized? Not all of them, but some were because they were so ill that they could not be treated at home. I do not believe that hospitalization was the factor causing relief because they had not cleared up on previous admissions for longer periods, and again these patients admitted to hospital have remained well by the use of the cortical hormone, instead of being repeatedly returning for readmission.

We realize that this presentation is a bit previous, but circumstances not of our control have forced us to this alternative.

Studies in Absorption of Undigested Protein in Human Beings. VII. Absorption of Unaltered Protein Introduced by Duodenal Tube Into the Abnormal Gastrointestinal Tract. MATTHEW WALZER, M.D., and IRVING GRAY, M.D., Brooklyn, N. Y. (Abstract.)

The absorption of unaltered protein was studied with the technic previously employed in this series. The subjects were sensitized with an intracutaneous injection of 0.05 c.c. of human serum containing reagins for peanut. The test meal, administered before breakfast, consisted of 10 grams of raw ground peanuts in 30 c.c. of water. The appearance of a local reaction, consisting of erythema, wheal, and pruritus, marked the entrance of unaltered peanut protein into the circulation. In the present series of 32 cases, the protein meal was administered by tube directly into the duodenum. The subjects studied all suffered from some functional or organic disturbance of the gastrointestinal tract. Patients with neoplasms or with atopic illnesses were omitted from the statistical studies.

TABLE I

INFLUENCE OF GASTRIC ACIDITY ON RATE OF ABSORPTION OF UNALTERED PROTEIN FOLLOWING ORAL ADMINISTRATION

DEGREE OF GASTRIC ACIDITY	NO. OF CASES TESTED	ABSORPTION TIME IN MINUTES		
		Minimum	Maximum	Average
Anacidity	4	8	14	11.7
Hypoacidity	13	12	19	15.9
Normal acidity	9	14	23	18.7
Hyperacidity	14	19	38	27.5

Test meal 10 grams of raw ground peanuts, 30 c.c. of water, 1 gram sugar, and 0.05 c.c. of oil of cloves. Sensitization with 0.05 c.c. of "C" (peanut) serum in 1-10 dilution.

In a previous study of 40 cases with gastrointestinal diseases (Table I) it was found that the rate of absorption of unaltered peanut protein, administered orally, was directly influenced by the degree of gastric acidity. Absorption was retarded in cases with hyperacidity

and accelerated in cases with hypoacidity or anacidity. In the present series similar results were obtained, even though the peanut meal was introduced directly into the duodenum.

TABLE II

COMPARISON OF ABSORPTION RATES FOLLOWING ORAL AND DUODENAL ADMINISTRATION OF PROTEIN

CASE NO.	DIAGNOSIS	ABSORPTION TIME IN MINUTES	
		Oral	Duodenal
21	Chronic cholelithiasis	18	16
22	Pyloric ulcer	33	23
23	Cholecystectomy	27	30
24	Duodenal ulcer	33	25
25	Colitis	27	22
26	Ulcerative colitis	37	20
27	Duodenal ulcer	26	19
28	Arteriosclerosis	21	19
29	Chronic cholecystitis	33	19
30	Migraine	24	23
31	Carcinoma colon	18	15
32	Chronic cholecystitis	9	13
33	Duodenal ulcer	32	20
34	Chronic gastritis	16	13
35	Gastric neurosis	14	13
	Average	24.5	19.3
Average for entire series of 32 duodenal cases			19.1

TABLE III

INFLUENCE OF GASTRIC ACIDITY ON RATE OF ABSORPTION OF UNALTERED PROTEIN FROM DUODENUM (32 CASES)

DEGREE OF GASTRIC ACIDITY	NO. OF CASES	ABSORPTION TIME IN MINUTES		
		Minimum	Maximum	Average
Hypoacidity	10	11	24	16.1
Normal acidity	13	12	30	17.5
Hyperacidity	9	14	31	24.0

TABLE IV

RELATION OF GASTRIC ACIDITY TO ABSORPTION RATES IN ORAL AND DUODENAL ADMINISTRATION OF PROTEIN (15 CASES)

DEGREE OF GASTRIC ACIDITY	NO. OF CASES	ABSORPTION TIME IN MINUTES		
Duodenal Administration				
		Minimum	Maximum	Average
Hypoacidity	4	13	22	15.8
Normal acidity	6	13	23	18.3
Hyperacidity	5	19	30	23.4
Oral Administration				
Hypoacidity	4	9	27	17.5
Normal acidity	6	18	37	24.5
Hyperacidity	5	26	33	30.2

The average absorption rates with gastric hypoacidity, normal acidity, and hyperacidity in the duodenal series of 32 cases were 16.1, 17.5, and 24 minutes respectively (Table III). In a series of 15 cases which

were studied both by oral and by duodenal administration, the average duodenal absorption time was 19.3 minutes as compared with 24.5 minutes by the oral route (Table II). In this group the average rates for cases of hypo-, normal, and hyperacidity, following oral administration, were 17.5, 24.5, and 30.2 minutes respectively, as compared with 15.8, 18.3, and 23.4 minutes (Table IV) for the duodenal route.

In three cases of gastric carcinoma with incomplete pyloric obstruction and with anacidity, absorption times were prolonged to 46, 51, and 62 minutes (Table V), thus suggesting an absence of absorption

TABLE V

INFLUENCE OF MECHANICAL FACTORS ON ABSORPTION OF UNALTERED PROTEIN ORAL ADMINISTRATION

GASTRIC CARCINOMAS WITH INCOMPLETE PYLORIC OBSTRUCTION	ABSORPTION TIME IN MINUTES
Case 1	46
Case 2	51
Case 3	62
Average of 13 hypoacidity cases of same series	16.9
POSTERIOR GASTROENTEROSTOMIES FOR CHRONIC DUODENAL ULCER	
Case 4	23
Case 5	26
Average of 14 hyperacidity cases in same series	27.5
Average of 9 normal acidity cases in same series	18.7

through the gastric mucosa, and establishing the possibility of mechanical factors retarding the absorption of unaltered protein by delaying the emptying of the stomach. On the other hand, in two cases with posterior gastroenterostomies for chronic duodenal ulcers, despite the rapid emptying time of the stomach, the absorption times were five and eight minutes longer than the normal rate because of the influence of the hyperacidity associated with these illnesses. Hence, with the exception of neoplastic obstruction at the pylorus, the emptying time of the stomach was found to be secondary in importance to gastric acidity in determining the rate of absorption of unaltered protein from the upper gastrointestinal tract.

DISCUSSION

DR. HARRY ALEXANDER, St. Louis.—This paper is very difficult to discuss because so little, apparently, is known about protein absorption from the bowel. It has been recognized for many years that small amounts of protein substances ingested may be identified unaltered in the systemic blood stream. That was found out very soon after the discovery of the precipitin test and has been confirmed again

and again. But how this protein arrives in the systemic blood from the bowel has been a matter of some debate and very little experimentation because the methods of detection and method of experiment were all too difficult until Dr. Walzer discovered the method which he used in this particular experiment; namely, that of giving normal individuals certain substances and then testing their own skins by means of reagins for the specific protein.

That opened the possibility of finding out how the ingested proteins reach the systemic blood. It has been recently shown that contrary to the earlier presumptions they do not go through the liver at all but travel via the thoracic duct. That work, which was made possible by Dr. Walzer's experiment, is part of a program that is being established in some clinics to follow out and see what does happen to the proteins absorbed from the bowel. This work that Dr. Walzer presents here is part of such a program.

The effect of acid upon the absorption of protein is entirely obscure to me. I am sure that if Dr. Walzer or Dr. Gray knew what happens they would have stated so. The interesting thing is that when the peanut meal is inserted in the duodenum, it contacts the alkaline juices and is not directly exposed to the acid gastric secretion.

It is known that hydrochloric acid has certain remote effects on digestion. It has something to do with the speed with which bile accumulates in the gallbladder and flows through the common duct. It has something to do with motility in cases of gastrogenic diarrhea. But how it acts is not yet understood.

Before accepting the suggestion in this paper, that the absorption of protein from the bowel is influenced by acid, I think there is a possibility that the protein may be absorbed at a normal rate. What happens is a delay of wheal formation in the skin because of this acidity. All of us have had varied experience in this regard. There are certain cases of urticaria that respond to the ingestion of hydrochloric acid. Also, if one takes a dog and ties off his pyloris, he loses all his hydrochloric acid by vomiting and goes into gastric tetany. A histamine wheal placed on the skin and compared with one placed there before he went into gastric tetany shows that after he lost acid the wheal became enormously increased. The clue to what happens is found in parathyroid tetany. When the calcium does not become readily ionized, a histamine wheal is very large. The degree of acidity or hydrogen ion concentration affects the ionization of calcium likewise. If you give hydrochloric acid in such cases, the wheal becomes smaller. The conclusion seems to be that the influence of acidity has something to do with the diffusibility of calcium in the skin.

I think therefore before it is accepted that the effect obtained by Dr. Walzer is due to slow absorption, it might be interesting to take animals or men and place histamine wheals on the skin and give them hydrochloric acid on an empty stomach without any meal at all and see the influence of that on the wheal formation of the skin.

May I say again that the importance of Dr. Walzer's method, as you may know as well as I do, has been recognized by physiologists as a very significant contribution to the physiology of digestion, and the field that it opens up is limitless.

Chemical Standardization of Pollen Extracts. ARTHUR F. COCA, M.D., and EDGAR L. MILFORD, Pearl River, N. Y. (For original article, see Vol. 7, page 337, May, 1936.)

DISCUSSION

DR. HOWARD OSGOOD, Buffalo.—I did not know this subject was going to come up; therefore I am really not prepared to discuss it. In our reports we brought up no question of standardization as such; we simply stated that the trichloracetic acid nitrogen was a better measure of the skin exciting activity found in the pollen extracts studied. Eventually it may prove to be a good method of standardization.

We have recently studied a ragweed extract, aged two years. This was compared in skin exciting activity with a fresh ragweed extract. The aged extract's activity was measured far more accurately by its content of nitrogen precipitated by trichloracetic acid than by total nitrogen or by nitrogen precipitated by phosphotungstic acid. The total nitrogen had dropped off some in the process of aging, and the phosphotungstic acid nitrogen had dropped off considerably. The trichloracetic acid nitrogen had dropped off to about 20 per cent of the original content. The pollen was aged for a year in the ice box, and a year at room temperature.

This question of standardization is one that is open to discussion. We are trying to measure chemically a biologic activity. Until we have determined the exact chemical nature of the allergic substance in any given extract, we cannot measure that substance exactly by chemical means. However, if we can find a fraction of the protein nitrogen or of the carbohydrate, or whatnot, in an extract which measures fairly accurately the skin exciting or allergic activity, I think we may be justified in using that chemically determinable substance as an approximate measure of the allergic activity.

Otherwise we have two alternatives: either (1) using a biologic method of standardization, such as is used in toxoids, which is not practicable in pollen extracts; or (2) using the simple weight or dilution basis of standardization. We know the latter is a perfectly useful method. We do not know, when we change from one pollen extract to a fresh extract of the same pollen, how the fresh is going to compare with the old in strength. If we can find a chemical fraction present in both extracts which parallels the skin and allergic activity, we have approached the matter of analyzing the biologic activity by an approximate chemical means.

I was very much interested in what Dr. Coca had to say. As far as the extract that he mentioned is concerned, we have worked only with timothy and ragweed pollen extracts. We do not want to imply that the same method may be applied to other allergenic substances, or extracts of other allergenic substances. We have to go step by step, and only apply a method where we find that, by actual experiment and study, it is feasible.

DR. ARTHUR STULL, New York City.—The work reported today by Dr. Coca and Mr. Milford is of special interest in showing the difficulties arising in quantitatively determining protein. In choosing a protein precipitant, it is important to select one which will give a

quantitative precipitation of the protein in the presence of other nitrogenous material without the precipitation of nonprotein material. Trichloracetic acid has not been generally used for quantitative protein determinations where appreciable amounts of gums are present, since they interfere with its use as a protein precipitant. Dr. Coca has emphasized these facts in his study of the bean extract and has shown that, previous to dialysis, material in the bean extract even prevented complete precipitation by phosphotungstic acid, although it gave quantitative precipitation after the removal of these substances. However, it cannot be assumed that, since phosphotungstic acid and trichloracetic acid do not give quantitative precipitation of protein in a bean extract, they cannot be used to determine protein in extracts of pollen of such very different chemical composition. It has been our experience with certain pollen extracts that trichloracetic acid failed to quantitatively precipitate protein which phosphotungstic acid accomplished.

I do not agree with Dr. Coca's original premise that neither enzymes nor toxins have been proved to be protein in nature. The foremost chemical work of the past five years by experienced workers in separate laboratories has given direct chemical evidence of the protein nature of enzymes. Crystalline proteins of constant chemical composition and constant enzymatic activity have been isolated by Sumner[1] in the case of urase in 1926, by Northrop[2] with pepsin in 1930, by Caldwell, Booher and Sherman[3] in the case of amylase in 1931, by Northrop and Kunitz[4] in the case of trypsin and chymo-trypsin[5] in 1933, and by Tauber and Kleiner[6] in the case of rennin in 1934. There is no doubt of the protein nature of these enzymes.

The direct evidence in regard to toxins favors their protein nature, particularly the recent work of Eaton,[7] who showed that purified diphtheria toxin appears to be a protein of more complex structure than the medium in which it was formed.

Dr. Coca has shown that the excitant of hay fever in pollens possesses two properties of protein; namely, large molecular size and antigenic property. The antigenic property has since been further confirmed by Burky[8] and by Bernstein.[9] There is considerable doubt if anything but protein is antigenic. Spain and Newell[10] have confirmed its large molecular size. The work of Grove and Coca[11] on the digestibility of pollen extract without loss of activity did not disprove its protein nature, particularly since the subsequent work of Melli,[12] Bouillenne and Bouillenne,[13] Loeb,[14] Moore and Unger[15] failed to confirm it and on the contrary has shown that enzymatic digestion of pollen extracts inactivated or decreased their activity. Moore and Unger[15] showed that enzymatic digestion of pollen extract did not affect the reducing sugars but reduced the allergic activity and therefore concluded the active substance was protein in nature.

The early work of Kammann,[16] Dunbar,[17] Koessler,[18] Heyl,[19] Bauman, Chudnoff and Mackenzie[20] and the more recent work of Bernton, Jones and Csonka,[21] Moore, Cromwell and Moore,[22] Johnson and Rappaport,[23] Adelsberger,[24] Spain and Newell[10] has supported the protein nature of the allergic material in pollen. Work from our laboratory[25] supporting the protein nature of the pollen allergen has been confirmed by Weyland and Ripke[26] at Elberfeld Physiological Institute, where they have repeated our work with similar findings on timothy pollen.

In reviewing the literature there is ample support from numerous independent workers for the protein nature of the pollen allergen. Therefore, standardization of pollen extract based upon the protein content represents an improvement upon methods not related to the active agent, namely, protein. Spain and Newell[10] confirmed the fact that the nitrogen not precipitated by phosphotungstic acid was inactive. Since approximately 50 per cent of the nitrogen in pollen extracts is not precipitated by phosphotungstic acid and is allergically inactive, how is it possible to argue that a total nitrogen standard is more accurate than a protein or phosphotungstic acid determination?

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DISCUSSION

DR. COCA.—Dr. Stull has made an extensive digression from the subject of our paper to review the literature concerning the protein nature of the crystalline enzymes of Northrop. The highly interesting experiments of Northrop argue strongly for a protein nature of pepsin and trypsin. However, they have not yet answered the objection made by Willstätter, published in 1932, describing powerful solutions of pepsin in which no protein whatever could be detected by any known chemical means. Dr. Stull's argument does not directly relate to the

subject of our paper, and it leaves still unaffected the fact that there is a group of large molecular, highly antigenic substances, which, like the pollen excitant, have not yet been identified as proteins.

As to the difference between bean extract and pollen extract, this we can really concede, the difference being that at least 99 per cent of the nitrogenous matter and at least 90 per cent of the phosphotungstic acid-precipitable substance in these extracts is not native protein. It is a rapidly dialyzable small molecular nitrogenous substance which is inert in the human skin and has nothing to do with hay fever. It is therefore inconceivable to me how any method that determines, as does the phosphotungstic acid precipitation, this inert nitrogenous matter, can be used as a standardization method for the excitant which quite possibly may be of a protein nature or may not.

Annual Review

ALLERGIC DISEASES IN CHILDHOOD

Review of the Literature

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THE observation of infants and children would seem to offer an opportunity to study the nature of certain diseases in relatively pure or uncomplicated states. The cumulative results from diverse insults to the human organism, which confuse the adult picture, usually are absent in the young. Hereditary factors, on the other hand, are more obvious and the usual home relations afford information more accurate with regard to family history and less subjective with regard to symptomatology. Hence, it has been expected that in the field of juvenile allergy etiologic factors and preventive measures could be discovered more readily.

The problem of etiology and prevention is not, however, easily solved. The marked lability of infants as a group affords no gauge for the reactions which may be seen in older children or adults. All too frequently natural processes, or at least factors beyond the knowledge and intent of medical treatment, will alter the nature and severity of the later manifestations considerably. (Nervous and psychogenic factors may complicate the adolescent period.) The defense mechanisms with which allergy is somewhat allied are poorly established in infants. In early infancy there may be protection from some diseases because of transmission of maternal immunity, but this is of short duration. The inherent immune bodies (judged by precipitins, etc.) are developed with age. Although extreme variability in the acquisition of immunity may be noted, time is an element of great import. The most recent discussions of the relationship of immunity and allergy are those of Schick,[1] who in contrast with Rich and his coworkers[2] would emphasize the similarity of the mechanism in allergy and immunity.

The skin of the young infant must undergo changes before it affords adequate protection. Early the skin is extremely sensitive to the physical agents, light, heat, cold and trauma, just as it is poorly resistant to infectious organisms. It would seem that a condition analogous to "street immunity" might be concerned with some allergies. But regardless of that possibility, the skin, from which we frequently expect information concerning specific allergic tests, is notably unre-

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liable under four to six months. There is a current interpretation that positive skin tests in general connote a skin sensitivity; although specific skin tests may be obscure or not interpretable under four months despite an eczema definitely related to food allergy. In older children papular urticaria (or lichen urticatus), which is classed logically as a skin manifestation, is notoriously without positive skin tests.

A few years ago Balyeat[3] reported positive tests in the newborn. At St. Louis Maternity Hospital I[4] was unable to confirm his results. In fact there was no correlation between skin tests and clinical manifestations of sensitivity even in those instances in which the mother gave definitely positive skin tests. Satisfactory passive transfer could be demonstrated on the skin of the newborn, but direct tests were not obtained. Unquestionably confusion has resulted from the false interpretation of the direct test reactions which, I feel, are the effect of trauma. By the same token, patch tests are uninterpretable if not useless in the very young. Hence, it would seem best to consider the clinical response and the specific skin test response as independent variables, frequently related in older children and adults. The skin test antibody or substance is identified with the globulin fraction of serum which usually is the vehicle for immune bodies.[5] In that respect certain phases of allergy find their parallel with the immunity mechanism; some individuals respond by developing immune bodies with increasing age; others are incapable of forming protective substances.

In the past, Coca[6] emphasized the hereditary factor in allergy (atopy), differentiating it from anaphylaxis largely on this basis and on the absence of demonstrable "antibodies." However, certain forms of "altered reactivity" such as primrose dermatitis, induced in apparently nonallergic individuals, and passive transfer with its antibody-like "reagins" break down some of the differentiating features. Coca also emphasized the absence of anaphylaxis in man, but other reports suggest that violent allergic shock is the counterpart of anaphylaxis. On the other hand, an hereditary factor would seem involved in animal anaphylaxis since experimental inbreeding has produced strains more susceptible to anaphylaxis. It is little wonder, then, that not a few investigators accept Rackemann's[7] thesis that what we call allergy is but anaphylaxis in man.

Ratner[8] has emphasized the rôle of placental transmission. From experimental and clinical observation he concludes that infantile allergy is due to direct transference from an allergic mother. Interesting as the idea may seem, however, there has not been sufficient corroboration on the frequency of parallel skin tests in mother and offspring. Follow-up studies over a longer period of time are indicated because we are not able at present to differentiate or recognize infants who escape manifestations early in life or those who at a later date may develop marked evidence of sensitivity.

Worringer[9] has recently reviewed the various theories regarding the etiology of infantile allergy. His report that placental transmission cannot explain all the instances is convincing. Often the male germ plasm is at fault. Unquestionably heredity remains an important factor in the etiology of allergy. Transitory allergic manifestations and mild episodes, such as Vaughan[10] has discussed, suggest either that few if any families escape instances of allergic phenomena or that temporary acquisition is a frequent phenomenon. In this respect I would mention the numerous instances of reactions strongly suggesting an allergic basis which are seen in clinics for infants and children. They are for the most part temporary and minor and, except as the potential "handwriting on the wall," are disregarded. Mayerhofer[11] in the past year has suggested that a great many conditions seen in the newborn are of allergic origin. For example, melena, hydrocele, pylorospasm and toxic "erythemas" are cited. While the report may stimulate investigation of some of these little understood conditions, it is not convincing. There is the danger in glib acceptance of this and similar reports, of bringing disrepute to the proper study of allergy.

It is apparent from what has been said that we are not yet in a position to undertake the full program for prophylaxis of allergic disease that Glaser and Landau[12] expound. The program is fallible particularly with regard to hereditary control of allergy. The emphasis on maternal cravings during gestation, while perhaps a factor, is not, I believe, necessarily related to sensitization of the offspring. The avoidance of certain articles in the diet of the known allergic infant, on the contrary, is sound. It would seem that the present enthusiasm for early introduction of solid foods could well be avoided in the allergic infant. It was not many years ago that variety in the infant diet was not customarily allowed until almost the end of the first year. Too early an introduction of varied foods in the dietary of the allergic infant unquestionably adds confusion to the study of the allergic reactions. Perhaps some "minor allergies" in children could be avoided by waiting until the organism is more stable in its metabolic and immune reactions to make additions to the diet. A great deal, of course, depends on the individual infant and the nature of the allergic manifestations.

Infantile eczema has attracted a great deal of attention in the past year. Hopkins and Kesten[13] have reported their observations on a group of 75 patients varying in age from one to twenty-seven years. They find Ratner's[8] placental transmission theory and the theory of transmission through breast milk more acceptable than other theories in accounting for acquisition of sensitivity. They reviewed much that is already known regarding infantile ezcema, such as the frequency of positive egg tests, spontaneous "desensitization," etc. They are in

agreement with the reports of Taub and Zakon[14] and those of Figley and Parkhurst,[15] and feel that the patch test may be negative when a deeper infiltration by scratch or intracutaneous route is positive. From this they consider the rôle of wool, feathers, etc., as ingestants rather than accept them in the usual class of inhalants.

Concerning common foods frequently related to infantile eczema, Ratner[16] has verification for the beneficial effect of heat or evaporation processes. As a shock agent such processed milks show loss of antigenic properties, while as a food they are absorbed more slowly and with more complete digestion. As for the sugars, he finds the proteins of their source responsible for allergic responses. On this basis, malt extracts may produce symptoms in individuals sensitive to barley while purified sugars such as corn syrup and dextrimaltose cause no trouble. Addition of wheat germ to the diet may introduce the allergens of wheat. Blatt and Schapiro,[17] reporting a study of development of infants fed with the cereal mixture of Tisdall, Drake and Brown,[18] found no allergic manifestations in their group. The comment is of no great value, however, since we do not know the instance or percentage of allergic infants in their group or in which of them familial background would lead to suspicion of allergy.

Rittinger and his coworkers[19] have studied an infant food made from the soy bean. This milk substitute was first reported by Hill and Stuart.[20] At that time barley was incorporated in it, but, because of the frequency with which barley may give allergic reactions, cornstarch was substituted. The latest report is that of the growth of 235 infants given this feeding. Considering the apparent success, the report answers the possible criticism that protein of vegetable origin is not so good a tissue builder as an animal protein. The authors found some improvement from use of the milk substitute for infants with eczema which they attributed to the high ratio of unsaturated fatty acids in soy bean oil. The search for the ideal food for the infant with eczema is not new. Years ago a liver soup was suggested. More recently cemac was devised by Cohen and his coworkers.[21] The combination of a basic protein of animal origin and valuable ingredients of vegetable origin seems logical. So far no extensive study similar to that of sobee has been made. It is my opinion, however, that while certain instances of infantile eczema have been benefited by the use of milk substitute feedings, the quest for the ideal formula for infantile eczema presupposes milk sensitivity as the sole etiology. All too frequently results are disappointing because of neglect of other contributory factors. Many instances of improvement have followed local applications, the avoidance of soap, the reduction of scratching, and control of changes in temperature, etc. Often too it would seem that alteration of cow's milk itself, by boiling for example, is simpler, cheaper and more likely to give

ultimate tolerance without too great a departure from this important item in the juvenile diet. For obvious reasons elimination diets for the growing child must be more carefully arranged than those for the adult, whose reserves are greater and whose demands of growth need not be considered. Sweeping restrictions have been observed to make for nutritional edema and even scurvy in children. With such possibilities, would it not be wiser to maintain nutrition and risk a touch of eczema?

Returning to the field of investigation, it is to be recalled that Schloss[22] reported evidence, years ago, suggesting the absorption of undigested protein through the bowel wall. Since his first report, he and his coworkers have continued to study this phase of allergy. Others, particularly Walzer,[23] have confirmed this work by passive transfer and new methods of study. Tallerman[24] in England has in the past year reported evidence of a circulating reagin in the blood of infants with enteritis and suggests that the clinical toxic symptoms may be correlated with this finding. This thesis is exactly that previously suggested by Schloss, Anderson and Stuart.[25] Schloss and Johnson[26] have recently studied the precipitin and complement fixation tests, following initial ingestion of protein foods. An appreciable amount of antigen was found in the blood for several months even after antibodies had developed. As for the defense mechanism of the body, the authors postulate the development of impermeability, the alteration in digestive enzymes so that denaturization takes place, or the neutralization by some unknown immune action. It seems to me that the first hypothesis is untenable since normal individuals will give satisfactory passive transfer reactions when the reagin is given by mouth. In their discussion of the evolution of atopic dermatitis, Hill and Sulzberger[27] consider infantile eczema and neurodermatitis of older individuals. Their review is timely even though it adds nothing new to the study of eczema. Unfortunately, life histories of patients followed through infancy to adult life are not numerous, and without such studies we are forced to accept inadequate histories and have little chance to study the factors which make for alteration in symptoms and tests of allergic individuals. What might be expressed as a European opinion, is that of Schiff,[28] whose program is not that of the allergy enthusiast. Rather pessimistic as to an understanding of neurodermatitis, he advocates a raw fruit and vegetable diet. A practical program for the treatment of infantile eczema is found in the report of Van Rhee.[29] His discussion not only of allergy but of irritants such as soap, wool and feathers, and his discussion of ointments and local applications should be welcomed by the general practitioner.

For some time search has been made for blood chemical or metabolic equivalents in allergic conditions. The finding of such indices would, of course, be a great boon. While the traditional eosinophilia of the

blood has been disappointing because of its variability and constancy, Hansel[30] has emphasized the importance of nasal mucosal eosinophilia. The report of Cowie and Jiminez[31] is confirmatory and is from a pediatric clinic. Another cytologic index has been noted by Vaughan,[32] who finds a marked drop in the total white cell count following ingestion of offending foods. It would appear, however that since normal infants show extreme variations in the white blood count (Washburn), the value of the leucopenic index is negligible in young infants. The sedimentation rate of red cells has been studied with relation to allergy, and the results so far are not striking or sharp enough to warrant enthusiasm. Further investigations of hypochlorhydria, which was first reported by Oriel[33] and other English investigators, have shown that gastric acidity is inconstant in the young allergic patient, and in all likelihood hypochlorhydria is a secondary rather than a causal factor. With considerable theoretical indication Cohen and Rudolph[34] have studied the correlation of adrenal function by our present limited and indirect means, but they report no striking results.

The most recent study has been that of the blood fats. Investigators at the University of Minnesota made blood fat determinations in convulsive conditions. In the course of this study Hansen[35] first reported the lowering of unsaturated fatty acids in infantile eczema. From a practical standpoint he advocated linseed oil or corn oil in the treatment of such cases. Cornbleet and Pace[36] were enthusiastic from an empirical trial of this procedure. Rittinger, Dembo and Torrey[19] suggest that soy bean milk is of value in infantile eczema because of its high content of unsaturated fatty acids. However, Faber and Roberts,[37] with observation of a small series of patients, were not impressed with the difference in determinations in eczematous and normal infants. Taub and Zakon[14] were likewise skeptical of the significance of lowered fatty acid serum content and warn against the clinical use of linseed oil which might seriously upset the cottonseed sensitive patient.

It has been common observation that infantile eczema undergoes apparent improvement during infection. Various hypotheses have been expressed suggesting water loss, fever effect, etc. More recently Stoesser[38] reports a lowering of the cholesterol fraction in nonallergic infants with infection which is less marked in older children and in those infants with eczema. While perhaps his series is too small to warrant conclusions, the effect of infection on both the cholesterol value and the iodine number of the fatty acids warrants study. The type of infecting organism should also be studied. For while there may be improvement in the skin manifestations when infection complicates infantile eczema, there seems, on the other hand, to be a tendency to develop respiratory allergy in those instances of infection in the respiratory tract. Mention should also be made of Burky's[39] studies, showing the ability of staphylococcus toxin to alter the antigenicity of substances.

Of recent date no reports have been made that offer an answer to the cause of the shift from the skin to the respiratory tract as the shock organ in the allergic child. Even though more instances of infantile asthma are observed, the sequence of childhood asthma for the eczematous infant remains the common or expected course. As mentioned, Schloss[26] implies a defense mechanism against offending foods. Does the same hold for offending inhalants when absorption is by the respiratory tract?

In early textbooks the bronchitis of eczematous infants was properly heralded as the overture to asthma. Infections, notably pertussis, were seen to play some part. Perhaps the irritation of the respiratory tract and certain bacterial toxins remove the body defense. Not all infections, however, can be considered as necessarily provocative. Like surgical manipulations, the effect on the allergic individual varies so as to make sweeping statements unwise. I recall two brothers of whom the eight-year-old had had asthma since infancy while the younger six-year-old brother had been free from symptoms. They developed measles simultaneously; thereafter the older boy was apparently free from asthma while the younger one was subject to definite asthmatic attacks. The results of much of our empirical treatment parallel the above illustration. For example, there has been an enthusiasm in the past for adenotonsillectomy, and at present emphasis is being placed on the aggravation of asthma by this procedure. Bullen[40] and others would avoid tonsillectomy in the known asthmatic patient. The Australian writers, Maddox and Back,[41] call attention to "the well known freedom from asthma for as long as a year post-tonsillectomy" and a year ago Coca[42] reported "improvement following surgical operations" even though the mechanism was not clear. Hence, it would seem logical to advise tonsillectomy in the asthmatic person solely on the indications apart from the presence of asthma.

Miller, Piness, Feingold and Friedman[43] report many instances of febrile reaction and pulmonary symptoms in which the course and the roentgenologic studies suggest a possible allergic consolidation of the lung. Unfortunately, no pathologic study is available. The good prognosis defeats this necessary correlation. The idea, however, is stimulating. In the first place, the possible parallel with the more chronic epituberculous process is suggested, and, on the other hand, the possible rôle of mucous plugs with atelectasis must be borne in mind. One is reminded of the twenty-four-hour pneumonias which are seen in children's wards. Yet in the instance described by Miller and his coworkers it is difficult to know what part bacteria may play in the pathologic condition.

I have found it difficult to understand many of the reported empirical treatments. As stated earlier, various shock episodes will alter the

allergic manifestations. Some infections, some surgical measures, and many procedures in treatment would fall in this category. Asthma has at times responded to glucose given intravenously (Matzger[44]) yet Wegierko[45] emphasizes the induction of hypoglycemia as beneficial. Calcium therapy has been repeatedly advocated; yet there is little evidence at the present time to consider calcium other than of empirical value. Lay opinion relishes the bizarre and mysterious. Perhaps this accounts for considerable enthusiasm for iontophoresis despite the disparaging studies of Alexander.[46] The use of histamine in the study of urticaria and the cell-produced toxin described by Lewis[47] as a histamine-like substance has led to the use of histamine in treatment. However, so far as children are concerned, I feel that great caution should be exercised before adopting the histamine therapy advocated by Dzsinich.[48] Maddox and Back[41] have in the past year reported on the use of autoseral therapy in juvenile asthma. They conclude the treatment is of no benefit.

A more scientific attempt at therapy is that of Cooke and his coworkers[49] who injected the blood from treated hay fever patients into recipients who were sensitive to the same pollens but untreated. Both transfusion and intramuscular injection seemed of benefit. They found no diminution of the skin test reaction but a lessened passive transfer reaction in the recipient and suggested a "blocking mechanism." Before accepting a possible specific factor it would be well to note the possible effect of blood transfusion or injection from either non-hay fever or nontreated hay fever donors.

Experience has shown that repeated pollen surveys are necessary to keep informed with regard to the variation and significance of change in flora from altered climatic and cultivation conditions. The earlier conclusions that infants and young children never react to inhalants would seem erroneous from the studies of Piness[50] and his group. Indeed it is surprising how often positive pollen tests have been found by these workers in small infants. Without discounting the thesis of virus or infectious origin of coughs and colds, adequate appreciation of the possibility for their occurrence on an allergic basis will be rewarded. The report of Clein[51] on this problem is helpful. In the same manner variations in modern living are constantly introducing new and potential offenders in the whole field of allergy. A recent outstanding contribution is that of Cohen and coworkers[52] which shows the development of an allergen by the aging of cotton linters.

Another important investigation is that of Benjamin and his coworkers.[53] They have considerable evidence to support the thesis that the allergenic action of pollens is related to a linkage of small molecules with large, usually protein, molecules. The Scandinavian research[54] in the field of colloidal chemistry establishes a parallel in the production of protamine insulinate.

For some time Waldbott[55] has challenged the acceptance of so-called thymic death. Although it is too early to rule out a possible thymic hormone factor, he has strong evidence to show that some of the fatalities are instances of anaphylaxis. The work of Boyd[56] had previously shown little or no involution of the thymus gland in healthy infants after sudden death.

Only rarely can the usual pathologic correlation be obtained in the study of allergy, particularly juvenile allergy. This has led to considerable skepticism on the part of some in the profession, to imaginative flight-of-ideas on the part of others, and to the challenge of the new frontier in medicine for those sincerely interested in the problems of allergy.

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Selected Abstracts

Asthma

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Intramuscular Injections of Ether in Treatment of Bronchial Asthma. Gurevitch, E. Y.: Klin. Med. **13:** 1554, 1935.

The author treated 80 patients having typical bronchial asthma with injections of ether. Gradually increasing doses of pure ether were injected into the upper outer quadrant of the gluteus muscle. The first three injections were given daily, the next three every third or fourth day and the last two every fourth or fifth day. In the patients having acute attacks or in those with status asthmaticus a marked improvement was frequently noticed after the first injection. Of 48 patients with acute attacks one injection stopped the attack in 25 cases; general improvement was noticed in 15 cases and failure in 8 cases. Of the 32 with status asthmaticus 25 benefited greatly by this treatment.

Even in patients with long standing asthma with secondary bronchitis and emphysema the results were very encouraging: the sputum became more liquefied and easier to expectorate; dyspnea subsided, and the bronchitis cleared. The author hesitates to say much about permanency of cures. Those who were observed remained well six to twelve months after treatment. Even in those who had a relapse the recurrent attacks were lighter and of shorter duration.

Endotracheal Treatment of Bronchial Asthma. Yaroslavsky, V.: Sovet. vrach. gaz., p. 1675, Nov. 15, 1935.

In 1911 Ephraim published a method of endotracheal treatment of asthma, claiming complete and permanent cure in 47 cases out of 52. Yaroslavsky modified this technic by employing a special laryngeal syringe instead of a bronchoscope tube. The larynx, the pharynx, the root of the tongue, the epiglottis, and the vocal opening are thoroughly anesthetized with the following solution: cocaine hydrochloride 1.25 gm.; adrenalin 1:1,000, 1.25 c.c.; potassium sulphate, 2 per cent, 5 c.c.; phenol 1.2 per cent, to volume of 25 c.c. Then 1 c.c. to 2 c.c. of the above solution which has been diluted five times with 0.5 per cent phenol is injected into the trachea. The patient is then seated on a chair and advised to lean sidewise against the back of another chair placed under his right axilla and to breathe quietly. In this position half the medicinal solution (5 c.c. to 10 c.c.) is injected with the laryngeal syringe. Then the patient's position is changed to the left side, and the balance is injected. The patient is then put to bed and advised to desist from coughing. The medicinal solution consists of novocaine, 0.2 gm.; adrenalin (1:1,000) 1.0 c.c.; physiologic NaCl, 9.0 c.c. The dose of novocaine is gradually increased to 0.5 gm.

The treatments are given at intervals of one to four weeks, from three to ten times. The author claims very good results by this method.

Results Obtained in Treatment of Hay Fever With Pollen Extracts. Ellis, R. V.: Minnesota Med. **19**: 507, 1936.

Ellis deprecates the conventional division of hay fever into seasons. Since there is considerable overlapping and since multiple sensitivity is the rule (85 per cent), good results are not to be obtained unless the treatment is based on a complete understanding of the varieties of plants causing hay fever in the region of the patient. In a series of 143 carefully studied hay fever patients in which the diagnosis and the treatments were supervised by the author during 1935, 40 per cent obtained complete relief, 30.8 per cent marked relief, 16 per cent fair relief, 9.8 per cent slight relief and failure in 3.4 per cent. Neither the number of injections nor the duration of the treatment correlated as well with the results obtained as did the maximum dosages used. Of 41 of these patients who had had previous treatment over an average of 2.5 years 87.8 per cent obtained better results than with any previous treatment. Ellis feels that this improvement in results is due to the increased accuracy of the specific treatment.

Studies in Asthma. XIX. The Nose and Throat in Five Hundred Cases of Asthma. Weille, F. L.: New England J. Med. **215**: 235, 1936.

In a complete study of 500 asthmatic patients Weille found sinusitis in 362. Vasomotor rhinitis was observed in 223 patients, almost equally in intrinsic and extrinsic asthma, while sinusitis was slightly more common in the intrinsic group. Other lesions found were polyps in 211, surgically deviated septum in 95, severe chronic tonsillitis in 35, and abscessed teeth in 84. Sinus operations were done in 100 patients of which 17 were intranasal antrum operations, 41 radical antrum, 30 intranasal ethmoid, 5 external ethmoid, and 17 sphenoids and external frontals. More or less improvement in the asthma resulted in 66 per cent of those having sinus operations. The improvement was the same whether the asthma was intrinsic or extrinsic. A higher percentage of improvement in asthma followed conservative nasal surgery rather than very drastic operations.

In 186 patients chronic tonsillitis was diagnosed, of whom 35 had tonsillectomies. In 25 there was improvement in the asthma. In 84 patients abscessed teeth were discovered. Of these 59 had the abscessed teeth extracted. In the latter group 39 had improvement in their asthma. In 36 patients in whom bronchoscopy was done as a part of their treatment 12 were improved and 3 were cured.

There were 290 patients who had no surgical treatment whatsoever, in spite of the fact that many of these were afflicted with sinusitis, chronic tonsillitis, or abscessed teeth. The proportion of results in this group treated only medically was about the same as that in the group treated surgically.

Roentgen Ray Treatment of Hay Fever. Hatchette, S.: New Orleans M. & S. J. **89**: 70, 1936.

Of 16 hay fever cases treated by x-ray over the nose, 12 received satisfactory results. Two patients with seasonal asthma and one with perennial rhinitis failed to obtain relief. Usually the treatment was administered during the season and consisted of two or more irradiations over the region of the nose, with the following factors: 100 KV., 3 ma., 2 mm. Al., and a field of 10 cm. × 10 cm.

Allergic Diseases Occurring With Tuberculosis. Wilson, R. A.: Southwestern Med. **20**: 331, 1936.

Among 321 cases of tuberculosis studied in the Southern Pacific Tuberculosis Sanatorium, Wilson found 17 with allergic manifestations. Of the latter, 12 had hay fever, 4 had asthma and 3 urticaria. The author thinks that there is no etiologic

relationship between the two conditions. He emphasizes the importance of the treatment of the allergy in the tuberculosis. He does not find pollen treatment harmful to the tuberculosis patient, while untreated allergy makes the prognosis of the tuberculosis more grave.

Causes, Diagnosis and Treatment of Hay Fever. Rosendahl, C. O., and Dahl, A. O.: Minnesota Med. **19**: 505, 1936.

These authors discuss the hay fever weeds of the Minnesota area based on their comprehensive surveys. While they admit that the ragweeds are of greatest importance, they call attention to the chenopods, which begin their season a little earlier than the ragweeds. It is further pointed out that too little attention has been paid to the artemisiae, such as wormwood, sagebrush, absinth, mugwort, and carpet sage. Their pollen counts are low, but they persist during July, August and September, reaching their height of pollen concentration after the middle of September.

The Treatment of Bronchial Asthma by Intratracheal Injections of Iodized Oil. Anderson, W.: N. Y. State J. Med. **36**: 1151, 1936.

Anderson has enlarged his original group of 60 asthmatic individuals treated by intratracheal injections of iodized oil to 260 in the present report. All the patients were of the chronic type, comprising both allergic patients and those whose asthma was caused by infection. Of the 200 uncomplicated cases 180 were completely relieved from one to eight years. The average time under treatment was ten months. In some patients the relief was obtained at once; in others there was gradual improvement, and some did not show any improvement until several months of treatment had been given.

The pharynx and the anterior and posterior pillars are sprayed with a 2 per cent nupercaine solution. This is followed by the instillation into the larynx of 2 c.c. or 3 c.c. of 5 per cent nupercaine. The iodized oil (lipiodol) is warmed to 110° F. and injected with a special syringe over the glottis. One side is injected at the first session and the opposite side a week later. The subsequent intervals between injections depend on the reactions and responses of the patient, and vary from one to several weeks.

Observations on History Taking in Allergy. Swineford, A.: Virginia M. Monthly **63**: 139, 1936.

The value of a thorough and detailed history in the investigation of allergic disease is emphasized. Among the most important points to be analyzed are the chief complaint, a description of and other data relating to the attacks, the presence of other allergic manifestations, the patient's environment and the effects of changes of it, the behavior of the patient to various foods, inhalants, drugs, contact substances and certain physical influences. In 50 allergic patients in whom complete histories were taken, the cardinal symptoms of allergic disease were attributed to foods 136 times, to physical agents 119 times, to inhalants 89 times, to drugs 8 times, and to contact substances 10 times. Focal infections were noted 38 times. The skin tests corresponded to the inhalant histories 41 times and to the food histories only 30 times.

Behavior of Immediate and Delayed Cutaneous Reactions in Asthmatic Patients. Stevens, F. A., and Jordain, L.: J. Immunol. **31**: 51, 1936.

In a series of asthmatic patients comprising both those who were sensitive to common allergens and those who were not, the authors made intracutaneous tests with

the nucleoproteins of cultures of the hemolytic streptococcus, *Streptococcus viridans, Micrococcus catarrhalis, Staphylococcus aureus,* and the influenza bacillus. Both the immediate and the delayed type of reactions were obtained with all the nucleoproteins; although the two types of reactions seldom occurred in the same individual with the same nucleoprotein. It is thought that the immediate reactions may have been due to traces of carbohydrates. The individual patient showed a definite tendency to react habitually to a bacterial nucleoprotein as he has reacted in the past. The authors call attention to the parallelism existing between these recurrent reactions of similar type and the recurrence of asthmatic attacks in infectious asthma following upper respiratory infections.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY

Allergy in Its Relation to Sympathetic Ophthalmia. Woods, Alan C.: N. Y. State J. Med. **67**: 85, 1936.

There are four widely different ideas on the etiology of sympathetic ophthalmia: (1) that the disease is caused by some unknown, undiscovered organism with a specific predilection for uveal tissue; (2) that it may be caused by a filtrable virus; (3) that it is a tuberculous or tuberculotoxic disease; and (4) that allergy is concerned in its etiology.

Following is the evidence, experimental, clinical, and pathological, in favor of allergy to uveal pigment (by absorption of the disintegrating uveal tissue in the exciting eye) being concerned in the etiology of sympathetic ophthalmia: (1) demonstration of the organ-specific properties of uveal pigment; (2) the ability of uveal pigment to act as an antigen in the homologous animal; (3) the production of an experimental uveal inflammation through use of uveal pigment as an antigen; (4) demonstration of immunologic reactions to pigment in patients who have suffered injuries which permit the absorption of uveal pigment; (5) the partial control of these observations in experimental animals; (6) the occurrence of hypersensitivity to pigment in certain cases of posttraumatic and postoperative uveitis; (7) the constant occurrence of pigment allergy in patients with sympathetic ophthalmia; (8) the results obtained in treatment of sympathetic ophthalmia by desensitization with pigment; (9) the phagocytosis of pigment in the pathologic picture; (10) and the exact similarity of the histologic pictures of pigment allergy and sympathetic ophthalmia.

Does this evidence indicate that pigment allergy is the actual and only cause of sympathetic ophthalmia? In view of findings of pigment allergy in certain cases of noninfectious, posttraumatic, and postoperative uveitis without sympathetic disease, and of one clear case in which there was uneventful healing of the uveal wound, the evidence does not indicate that pigment allergy is the actual and only cause of sympathetic ophthalmia, but does indicate that it is the predisposing factor necessary for the outbreak of sympathetic disease. The author believes that some other unknown factor acts as the actual spark which initiates the process, and that, once initiated, pigment allergy is again the factor which determines the characteristic histologic picture.

Dr. Conrad Berens is particularly interested in determining the importance of the skin tests to uveal pigment. What studies has Dr. Woods made of the relation of his positive and negative skin test cases to other forms of allergy in these individuals, especially those with allergic history? He offers a table showing reactions to uveal pigment in 73 cases, of which 25 control tests were positive at one-half hour, but only 4 of these were positive at twenty-four hours. One true case of sympathetic ophthalmia gave negative uveal pigment tests. In 4 cases the uveal pigment test was positive. He concludes that these tests have no clinical value and believes that, more important than hypersensitiveness to uveal pigment, is the sensitization of the patient to toxins from his own bacteria. In the few supposedly sympathetic ophthalmia cases he has seen, there has always been association of definite disease in the nasal accessory sinuses; and apparently the best results occurred when sinuses were properly cared for. Final evidence must be from experiments on human beings and in immunity. It is most necessary to use human beings because immunologic reactions seem to differ widely in man and in animals.

Hypersensitivity Diseases of Skin and Their Relations to Vegetative Nervous System. Marquardt, F.: Dermat. Wchnschr. **100**: 409, 1935.

The author tested 60 patients at the University of Cologne with atropine injected intravenously. Thirty-four of the patients had eczema, 20 had skin diseases other than eczema, and 6 had urticaria and urticaria factitia. The object was to discover by means of the pulse reaction the presence of hyper- and hypovagotonia, or of hyper- or hyposympathicotonia. Only 15 of the subjects were found normal in this respect, but among the three groups no striking differences could be found. Pure forms of hyper- or hypovagitonia and of hyper- or hyposympathicotonia and of hyperamphotonia were rare in any of the groups. Hypotonia was the more frequent in both systems. More normal cases were present in the noneczematous than in the eczematous group, 34.5 per cent against 17.5 per cent. No difference was found between allergic eczemas and other forms of eczema.

Marquardt next sought to determine whether sensitization to a particular substance alters the reactivity of the vegetative nervous system. The procedure was to test a normal subject with adrenalin, atropine, or pilocarpine, then to sensitize with paraphenylendiamin, and to retest. The reactivity to adrenalin and to atropine showed no important change; while the reactivity to pilocarpine was definitely heightened by sensitization.

This suggests that heightened response of the vegetative nervous system to pharmacologic excitants noted in allergic dermatoses is not the cause of the dermatosis but the consequence of the sensitization, or an accompanying phenomenon. The experiment does not necessarily mean that it is the parasympathetic that is always brought into a state of increased excitability by sensitization. Whether the parasympathetic or the sympathetic is thus affected probably depends on which exerts a natural predominance in the individual.

Purpura Hemorrhagica Caused by Gold and Arsenical Compounds. Hudson, E. H.: Lancet **2**: 74, 1935.

On the basis of two cases of hemorrhagic, thromboeytopenic purpura caused by gold and arsenic respectively, the author reviews the literature, without being able to find any definite reason for such a complication. Neither age, sex nor toxicity seems to be a determining factor. Of the 22 patients with gold purpura, 11 had undergone a previous course of treatment with gold salts suggesting a pos-

sibility of sensitization. In the author's case of gold purpura, the condition followed administration of a very small dose of the drug. In 12 of the 22 cases of gold purpura prodromal symptoms appeared, itching being the most frequent. Eosinophilia occurred in only 4 per cent as compared to a much higher incidence in other complications of gold therapy. There were 10 fatal cases. Also 10 of the 19 cases of arsenobenzol purpura were fatal. The marked anemia in these cases is not exclusively due to loss of blood, which may be considerable, especially in women. The blood platelets are diminished or absent. This fact is not of prognostic significance, however; whereas leucopenia indicates a grave prognosis in direct proportion to the predominance of nongranular over granular cells. No preventive measures are known, and great caution should be observed in administration of these drugs to patients with a history of allergic or other abnormal responses.

The most satisfactory treatment is blood transfusion. Liver extract may be given to stimulate blood regeneration. As gastric hemorrhage is not uncommon, a soft, easily digested diet supplemented by minced liver and fluids containing at least 4 ounces of glucose daily are recommended.

Refractory Condition of the Skin Toward Urticariogenous Stimuli. Eliasz, A.: Arch. f. Dermat. u. Syph. **173**: 37, 1935.

The author feels that such terms as lymphagogue and exudative effect were better discarded for the more exact designation urticariogenic effect. The Gröer-Hecht pharmacodynamic skin test is of value for the demonstration only of physiologic urticaria and not of pathologic urticaria. It has been experimentally demonstrated that under certain conditions the skin is refractory to urticariogenic stimuli. A discussion follows of the node of diffusion of urticariogenic substances in the skin and of the origin of the sharply circumscribed contour of the urticarial wheals. From his experiments with various drugs as to the negative phase of the reaction of normal skin to urticariogenic stimuli, the author concludes that the refractory stage following resorption of an urticarial wheal depends upon latent edema. Failure or weakening of the reaction after restoration of circulation in an extremity subjected to circulatory obstruction, is due to exhaustion of the elements sensitive to the urticariogenic substance. The refractory state developing at the periphery of the wheal is an expression of the dynamic effect of the urticariogenic substance in the presence of a normally functioning vascular apparatus.

Contribution to the Eczema Problem. Miescher, G.: Arch. f. Dermat. u. Syph. **173**: 117, 1935.

From a series of experiments with various substances including panthesin, mustard plaster, r-x pinenes, chemically pure calcium, croton oil, hydrochloric acid, tincture of cantharides and microbic substances, Miescher concludes that neither the histologic nor the clinical picture of a spongiotic vesicle can be considered pathognomonic of an *allergic* eczema reaction even though *characteristic of an eczematous* reaction; for this reaction can also be elicited by toxic (primary irritant) action alone. Also bouillon filtrates of various bacteria produced the clinical and histologic changes characteristic of eczema reactions, raising the question as to whether such reactions were identical with those of genuine allergic eczema or represented toxic effects similar to those produced by croton oil and hydrochloric acid. The leucocyte involvement and follicular site of the microbic reaction, noted also frequently in the croton oil reaction are usually absent in genuine eczema. Certain age factors

governing the frequency of the reactions would seem to support the assumption of antitoxic influences determining the appearance or nonappearance of microbin reactions. The conception of a toxin effect, the degree of which depends upon the antitoxin index of the end-organ would remove the *microbin* reaction from the general eczema reaction, placing it beside the croton oil reaction. Likewise in the individual processes in eczema, clinical and histologic eczema reactions should not be rigidly conceived as allergic but at least the possibility considered of a simple primary irritant or bacteriologic effect.

Concerning Sensitization of the Skin to Autoserum and to Autoblood. Bizzozer, E.: Arch. f. Dermat. u. Syph. **173**: 342, 1936.

Bizzozer briefly reviews the literature and then describes experiments performed on 25 patients. Repeated, superficial, intracutaneous injections of their own serum elicited reactions in 9 patients, particularly when injections were repeatedly made at the same site. Reactions consisted of small, indurated nodules which persisted from twenty to forty-five days; the histology was of clearly tuberculoid structure. In 2 of these patients, intracutaneous injection of autoblood elicited immediate formation of a large wheal which then made way for a little nodule. In a third patient, the nodule was formed without previous wheal formation. Because of the phenomena described and the tuberculoid structures, the author assumes that new (foreign) substances form in the serum—either outside of the organism or after injection; and that these substances can sensitize the skin to the serum of the donor himself and sometimes even to his own blood. The resultant reaction is probably attributable to an antigen-antibody reaction.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

On the Relation of Heterophile Antigen to Serum Sickness. Powell, H. M., Jamieson, W. A., and Kempf, G. E.: J. Immunol. **29**: 267, 1935.

The authors sought to prove that there was no foundation for the theory that the heterophile antigen contained in horse serum was responsible for the development of serum sickness. In previous experiments they used horse tetanus antitoxin globulin, in which the heterophile antigen had been neutralized by admixture with heterophile antibodies. This antitoxin injected into 250 subjects induced serum disease to the same degree and with the same frequency as did the untreated stock antitoxin. In the present experiment, rabbit heterophile antibody was added in excess to concentrated antitoxin. After two weeks the precipitate was removed by Berkefeld filtration. It was found that 60 per cent of the heterophile antibodies were neutralized by this procedure. Injections of this antitoxin into a rabbit failed to stimulate the formation of any new heterophile antibodies, showing the absence of heterophile antigen in the material. Yet when this preparation was injected into 39 human beings, 30 per cent of them developed serum disease. A study of the serums of five members of this series, three of whom had serum disease, revealed no relationship between the titer of heterophile antibodies and the presence of serum disease. Hence, the heterophile antigen in horse antiserum does not appear to be responsible for serum sickness.

Variations in the Susceptibility of Guinea Pigs to Reversed Passive Anaphylaxis. Zinsser, H., and Enders, J. F.: J. Immunol. **30**: 327, 1936.

Previous reports by Kellet had shown that reverse passive anaphylaxis could be induced in guinea pigs provided there was an interval of forty-five minutes between the preliminary injection of antigen and the sensitizing serum. The authors found this alleged prerequisite to be unessential. They obtained positive results when the interval between injections of antigen and serum was only ten minutes and even as low as one and one-half minutes. They found that the breed of guinea pig was much more important than the time factor. Among 22 guinea pigs of one breed, 16 gave positive reactions. Seven died in acute shock, five recovered after severe shock, and four others showed milder symptoms. Among 24 animals of another breed tested under the same experimental conditions, only one died and five showed mild symptoms. All technical variables were ruled out as possible factors in the results obtained. The authors do not consider that these findings negate the theory of a cellular seat of the anaphylactic reaction. They believe, however, that the rapidity with which these tissue cells can fix the sensitizing antibodies varies in different breds of guinea pigs.

Studies on Inflammation. XII. The Mechanism of Increased Capillary Permeability: A Critique of the Histamine Hypothesis. Menkin, V.: J. Exper. Med. **64**: 485, 1936.

It is pointed out by the author that inflammation is initiated not only by a dilatation of the capillary walls but also by direct injury to the cells lining these passages. He questions Lewis' hypothesis that histamine or a histamine-like substance is responsible for these phenomena. By injecting turpentine into the pleural cavities of dogs he obtains an inflammatory exudate. He is able to isolate from this a diffusible crystalline material, which, although it increases capillary permeability, behaves unlike histamine in several respects. He injects a small amount of the cell-free exudate intracutaneously into normal rabbits and follows this with an intravenous injection of trypan blue. In a characteristic fashion the dye rapidly filters through the capillary walls at the site at which the exudate has been introduced. In this manner the ability of the exudate to increase the permeability of the capillaries is demonstrated. Intracutaneous injections of histamine are not followed by the same type of dye patterns which occur with the use of the inflammatory exudate. Exudates also differ from histamine in their effect upon the isolated strip of guinea pig intestine. Exudates cause a relaxation of the strip, while histamine induces the opposite effect. Human exudates possess the same properties as do those obtained from experimental animals.

The Plurality of Streptococcal Toxins. Hooker, Sanford B.: New England J. Med. **215**: 68, 1936.

The author has found the agglutinative characteristics of streptococci to be of negligible value in the grouping of these organisms. For the purpose of stimulating investigation along other channels he briefly sketches the available information on other antigenic attributes of streptococci. His discussion includes: (1) *Hemotoxins.* These stimulate antilysin production and are probably of some clinical importance. (2) *Leukocidins.* These are probably not toxins, as some maintain. They are antiphagocytic and, being correlated with the virulence of the organisms, are of great clinical importance. They are not neutralized by the

ordinary antistreptococcic serums. (3) *Exotoxins.* These are exemplified in the true toxins of scarlet fever. They vary widely in their properties, not only in different strains but even in the same strain. Exotoxins have not solved the problem of streptococcic infection. They are not especially malignant weapons of the organism and are rarely the dominant influence in fatal infections. Antitoxic immunity, however, has definitely been demonstrated to be of some clinical significance in aiding recovery from infection. (4) *Endotoxins.* These are supposed to exist preformed in the bacterial cells and to be liberated on their disintegration. This concept is still theoretical and "cloaks our ignorance" of the subject. (5) *Polysaccharides.* These are complex carbohydrates in the class of haptens; i.e., they condition specific reactivity but lack true antigenic powers. They are associated with the organism's capsule or ectoplasm. They permit serologic separation of hemolytic streptococci into groups. (6) *Type-Specific Proteins.* These are extractable with dilute hydrochloric acid and allow separation of streptococci into subgroups and determine their behavior in relation to agglutination, precipitation, etc. They behave like haptens. (7) *Neucleoproteins.* These are antigenic but lack differential specificity among the various types of organisms. Their significance in immunity has still to be demonstrated. (8) *Fibrinolysins.* These possess the power of dissolving clotted human plasma and may be of clinical significance in preventing localization by the host of some types of streptococcic inflammation.

The author points out that some of the most important antigens are being neglected in the investigation of streptococcic infections and immunity.

Studies on the Sensitization of Animals With Simple Chemical Compounds. II. Landsteiner, K., and Jacobs, J.: J. Exper. Med. **64**: 625, 1936.

The authors investigated the basis for the regularity with which guinea pigs could be sensitized to certain chemical compounds. Sensitization experiments were carried out on guinea pigs with various chemical substances including benzyl chlorides, acyl chlorides, and urushiol. The latter is the offending principle in Japanese lacquer dermatitis and possibly in poison ivy and oak dermatitis. With urushiol, sensitization was accomplished by four skin applications within the period of two weeks. With the other chemical substances a much larger number of intracutaneous injections were given. Tests in some instances were made by application and in others by intracutaneous injections.

In studying chloro- and nitro-substitution products of benzine, it was found that antigenicity for the most part depended upon the lability of the Cl and NO_2 groups on treatment with alkali, and paralleled their ability to form substitution compounds with an organic base. Benzyl and acyl chlorides containing easily detachable chlorines were suspected of being good antigens and were actually proved to be so.

Protein compounds containing acyl radicals were prepared from mixtures of guinea pig serum and p-chlorobenzoyl chloride. In guinea pigs sensitized with the chlorides, an intravenous injection of the protein compound caused anaphylactic death. An intracutaneous test with the protein compound in these animals produced an immediate flare and wheal, followed by a large, pink edematous reaction the following day. Skin application of the compound produced delayed superficial, pink, elevated eruptions. This suggested to the authors that the superficial skin sensitization and the anaphylactic hypersensitiveness, both of which were induced by the same substance, were intimately associated states of allergic manifestation.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

The Reaction of the Nasal Mucus. Tweedie, A. R.: Acta oto-laryng, 24: 151, 1936.

This report represents a few further observations on the reaction of the nasal mucus. Previous findings, in general, were confirmed in this report. It was found that the normal nose possesses a mucus with a reaction varying from pH 6.5 to pH 7.4, and a nonculturable content. In acute rhinitis it was found that the normal reaction is not affected for some two or three days, and during this time no culturable content is present. After that time a culturable growth of the common inflammatory organisms is obtainable for some three weeks. It was stated that chronic rhinitis may exist in connection with purely mechanical factors, for example, obstructive deviation of the septum, postoperative conditions in clean cases, or only as the result of traumatic lesions; also in hay fever, so-called spasmodic rhinorrhea and asthma, and even in some cases of rhinitis associated with sinusitis and polyps or syphilis. In all these cases an unaltered reaction of the nasal mucus and a nonculturable content may be found. On the other hand, Tweedie states that a chronic rhinitis may show abnormal alkalinity and reveal a culturable content obtained on a medium corresponding to the reaction of the mucus or only demonstrable on a medium of greater alkalinity.

As far as cultures were concerned, no growth was obtained from any nose on a medium at pH 6.5, with the exception of *Staphylococcus aureus* and *Staphylococcus albus*, which grow freely on any medium. *Staphylococcus albus* was regarded merely as a result of contamination and not pathogenic. The usual findings are some forms of streptococcus. It was further stated that this bacterial growth in the nose, therefore, does not take place until and if the normal reaction of the nasal mucus becomes alkaline and the growth must thus be regarded as a secondary infection, only virulent when some other condition induces an alkaline reaction of the nasal mucus. It was also pointed out that a normal reaction of the mucus is not the only safeguard, since other factors must certainly take part, for example, lysozyme, the action of the cilia, and probably the presence of a structurally normal nose.

The Effect of Intranasal Phenol Application in Hay Fever. Quantitatively Studied by a New Intranasal Swab Test With Pollen Extracts. Vistreich, Fernand: Laryngoscope 46: 717, 1936.

The effect of intranasal phenol application was studied by Vistreich in 28 consecutive cases of early and late hay fever. The technic of this procedure was described in detail. It was stated that the treatment was not followed by stormy reactions or long convalescence. The results were reported as follows: 90 to 100 per cent relief was obtained in 75 per cent of the cases; 75 to 90 per cent relief in 8.3 per cent; 50 to 75 per cent relief in 12.5 per cent; and no relief in 4.2 per cent. By means of intranasal swab tests with serial dilutions of pollen extracts, it was noted that the treatment produced an actual decrease in the sensitivity of the nasal mucosa to pollen. By periodic testing it was found that this state of relative insensitiveness is not permanent. The average duration observed in this group of cases was approximately seven to eight weeks. This form of treatment was recommended as a palliative procedure in those patients with hay fever presenting themselves for treatment during the season. Also in patients who previously had had unsatisfactory results from allergic treatment. It was also recommended for those patients who do not tolerate well the hypodermic injections of pollen extracts.

The Incidence of Sinusitis and Nasal Polypi in Bronchial Asthma. Kelley, S. F.: Laryngoscope **46**: 692, 1936.

The incidence of sinusitis and nasal polyps in bronchial asthma was studied by Kelley. His report was based on an investigation of 100 cases of bronchial asthma. According to the x-ray examination, 89 per cent of the 100 patients showed a chronic hyperplastic sinusitis involving one or more of the sinuses. The remainder, or 11 per cent, showed no evidence of change. Sixty of the 89 patients with chronic hyperplastic sinusitis presented allergic nasal membranes; 23 of these patients were found to have nasal polyps. Kelley found that antral lavage revealed that in those cases with definite allergic reactions of the nasal membranes, the mucous content of the washings was relatively increased over that which was observed in cases with so-called simple hyperplastic membranes.

Surgical Indications in Disease of the Nasal Sinuses Due to Allergy. Mullin, W. V.: S. Clinics North America **15**: 839, 1935.

The surgical indications in disease of the nasal sinuses due to allergy were discussed by Mullin, and several illustrative cases were presented. His observations were based on a study of 216 patients. In this group it was noted that operations had been performed in 52 instances with no relief of symptoms, and no studies to determine the presence of allergy had been made. Mullin found it necessary to perform the same operations after an allergic condition was diagnosed and eliminated in only 16 instances. It is obvious that if operation had yielded relief, these patients would not have sought further treatment. In this group of patients, therefore, careful studies to determine allergic sensitivity might have eliminated more than two-thirds of the nasal operations to which they were subjected. According to Mullin's experience, allergy is a complication in between 30 and 35 per cent of the cases of chronic disease of the nasal sinuses. These observations of Mullin emphasize the importance of primary allergic studies in patients and the necessity of conservative surgical procedures. The report is very instructive and should be read by every one interested.

Pediatrics

UNDER THE DIRECTION OF FRANCIS S. SMYTH, M.D., SAN FRANCISCO

Allergy as the Cause of Frequent Colds and Chronic Coughs in Children. Clein, N. W.: Northwest Med. **35**: 347, 1936.

The author cites case illustrations when the investigation revealed allergy as the basis for frequent colds and coughs. The results as illustrated by sample case studies are striking. He emphasizes proper methods for recognizing allergy but does not give any comment on differential diagnosis or the percentage of probable allergy in a series of patients with the same vague complaints.

Allergy Due to Menotoxin of Pregnancy. Perlstein, M. A., and Matheson, A.: Am. J. Dis. Child. **52**: 303, 1936.

The authors report an instance of asthma in a four-and-one-half-year-old negro girl. The onset began with the onset of pregnancy in the mother and subse-

quent periodicity of the asthma coincided with the maternal periodic leucorrhea. Wheal formation was obtained when the patient was tested intradermally with an extract of the maternal leucorrheal discharge.

A Case of Asthma and Stammering in a Boy. Yearsley, M.: Brit. J. Child. Dis. **33**: 106, 1936.

With little or no consideration of the allergic background, the author reports the coincidence of asthma and stammering. Repeated nose and throat operations, adenotonsillectomy, and submucous resection were done. The patient improved after a period of considerable time and with some directions regarding posture. The improvement was attributed by the author to "correction of bad posture and general malcoordination after the restoration of an adequate nasal airway had been only partially successful"!

Dermatitis in Children With Disturbances of the General Condition and the Absorption of Food Elements. Brandt, T.: Acta dermat.-venereol. **17**: 513, 1936.

The author reports rather extensive studies of a condition described as "Acrodermatitis Continua (Hallopeau)" with a familial occurrence. The illustrations and many of the features suggest to those interested in allergy, an allergic basis. In two instances skin tests to milk were positive. The author apparently regards failure of the skin test as ruling out allergy. Various procedures, such as endocrine therapy, were without effect.

Infantile Eczema. The Relation of Specific Ingesta to Pruritis and Eczema. Rinkel, H. J.: Arch. Pediat. **53**: 559, 1936.

The author states that by careful correlation of the maternal diet with pruritis and eczema of her nursing infant, satisfactory control of the condition was obtained. One would like to hear of the continued observation of the patient before accepting the report in its entirety.

Allergic Manifestations to Cow's Milk. Kerley, C. G.: New York State J. Med. **36**: 1320, 1936.

The author discusses briefly the symptoms and treatment of this condition, in which he has been interested for years. His valuable clinical observations are now finding confirmation in the laboratory.

Infantile Eczema From Cod Liver Oil. Hoffman, S. J., and Ratner, H.: J. A. M. A. **107**: 494, 1936.

Two instances of infantile eczema definitely related to cod liver oil are reported. There was evidence of fish sensitivity in both, as well as a paternal background of allergy. Skin tests were not given.

Serum Lipids in Eczema and Dermatitis in Infants. Freudenberg, E., and Schornstein, L.: Ztschr. f. Kinderh. **57**: 675, 1936.

These investigators found considerably greater variation in the serum fat content of younger patients. Even in control groups the variability was too great to establish the expected curve of serum fat following ingestion. In general there

was an increase in serum fat with age in the first year, and the increase, while significant, was less in the eczematous infants. Total cholesterol increased with age in both normal and dermatitis patients, the latter falling within the normal range. Clinically, they feel that the fat-poor diet recommended for seborrheic dermatitis can well be used in instances of eczema with seborrheic dermatitis.

Miscellaneous

Hypersensitiveness to Cold; With Local and Systemic Manifestations of a Histamine-Like Character; Its Amenability to Treatment. Horton, B. T., Brown, G. E., and Roth, G. E.: J. A. M. A. **107**: 1263, 1936.

Twenty-two patients were observed at the Mayo Clinic during the past ten years who had hypersensitiveness to cold. They exhibited abnormal local and systemic reactions following exposure to cold, and the systemic reactions were so striking as to constitute a clinical entity. These reactions are similar to those produced by the injection of histamine or a histamine-like substance; and there is much clinical and experimental indication that such a substance is released by the tissues of these individuals on contact with cold.

Reactions were elicited by immersion of the affected part in water at 8 degrees for six minutes. There was first pallor followed by redness, swelling and increased local temperature on removal of the part from the cold environment. After a latent period of from three to six minutes, a characteristic systemic reaction developed, consisting of flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, a tendency to or actual development of syncope and transitory recovery in ten to fifteen minutes. If a tourniquet was placed proximal to the exposed part, no systemic reaction occurred until the tourniquet was released. The hands, arms, legs, face and body were recorded as involved in different individuals.

Of the 22 subjects, 14 had systemic reactions. Eleven of these had syncope which occurred in 9 while in swimming, and 4 had to be rescued from the water. From the literature 76 further cases were gathered. Twenty-nine of these had systemic reactions; 18 developed syncope, and in 15 this appeared while in swimming. Four had to be rescued.

Eosinophylic Myocarditis. Sikl, H.: Frankfurt. Ztschr. f. Path. **48**: 20, 1936.

The case of a thirty-six-year-old woman, who was given bismuth and neosalvarsan for questionable syphilis, is reported. She developed a marked dermatitis and eventually died of cardiac failure. Sections from the heart showed a diffuse myocarditis with marked eosinophilic infiltration and necrosis. Another patient, a twenty-two-year-old man, was given these drugs for the primary stage of syphilis, and developed a dermatitis. Death occurred apparently suddenly from cardiac failure. There was an acute eosinophilic myocarditis similar to that of the first case, with the exception that it was tuberculoid; and localized changes appeared in the small arteries of the heart, kidney and spleen. In neither case were tubercle bacilli or spirochetes found. The author quotes a similar instance reported by Stoeckenius, and believes the reaction is due to an allergy to salvarsan.

Reaction of Sensitized Dog's Kidney to Horse Serum Injected Into the Renal Artery. Parks, A. A., and Taussig, B. L.: Proc. Soc. Exper. Biol. & Med. 34: 889, 1936.

The rôle of allergy in the pathogenesis of glomerulonephritis has been a subject of experimental investigation for many years and offers an attractive theory of the etiology of this disease. There has been considerable controversy about it. Nine healthy dogs were given sensitizing injections of horse serum intravenously. From sixteen to twenty-one days later, 3 c.c. of horse serum were injected directly into the renal artery. After another interval of one to twenty-one days, the dogs were operated on, the uterus was exposed and small catheters were held in place. Separate specimens of urine were collected from each kidney. Phenolsulphonephthalein excretion was studied, and the response to diuresis from salyrgen noted, as well as detailed observations on the urine. The animals were killed and the kidneys examined. From such observations no essential pathologic findings appeared.